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| | | |
|---|---|---|
| NEWS 1 | | Web Page for STN Seminar Schedule - N. America |
| NEWS 2 | MAR 15 | WPIDS/WPIX enhanced with new FRAGHITSTR display format |
| NEWS 3 | MAR 16 | CASREACT coverage extended |
| NEWS 4 | MAR 20 | MARPAT now updated daily |
| NEWS 5 | MAR 22 | LWPI reloaded |
| NEWS 6 | MAR 30 | RDISCLOSURE reloaded with enhancements |
| NEWS 7 | APR 02 | JICST-EPLUS removed from database clusters and STN |
| NEWS 8 | APR 30 | GENBANK reloaded and enhanced with Genome Project ID field |
| NEWS 9 | APR 30 | CHEMCATS enhanced with 1.2 million new records |
| NEWS 10 | APR 30 | CA/CAplus enhanced with 1870-1889 U.S. patent records |
| NEWS 11 | APR 30 | INPADOC replaced by INPADOCDB on STN |
| NEWS 12 | MAY 01 | New CAS web site launched |
| NEWS 13 | MAY 08 | CA/CAplus Indian patent publication number format defined |
| NEWS 14 | MAY 14 | RDISCLOSURE on STN Easy enhanced with new search and display fields |
| NEWS 15 | MAY 21 | BIOSIS reloaded and enhanced with archival data |
| NEWS 16 | MAY 21 | TOXCENTER enhanced with BIOSIS reload |
| NEWS 17 | MAY 21 | CA/CAplus enhanced with additional kind codes for German patents |
| NEWS 18 | MAY 22 | CA/CAplus enhanced with IPC reclassification in Japanese patents |
| NEWS 19 | JUN 27 | CA/CAplus enhanced with pre-1967 CAS Registry Numbers |
| NEWS 20 | JUN 29 | STN Viewer now available |
| NEWS 21 | JUN 29 | STN Express, Version 8.2, now available |
| NEWS 22 | JUL 02 | LEMBASE coverage updated |
| NEWS 23 | JUL 02 | LMEDLINE coverage updated |
| NEWS 24 | JUL 02 | SCISEARCH enhanced with complete author names |
| NEWS 25 | JUL 02 | CHEMCATS accession numbers revised |
| NEWS 26 | JUL 02 | CA/CAplus enhanced with utility model patents from China |
| NEWS 27 | JUL 16 | CAplus enhanced with French and German abstracts |
| NEWS 28 | JUL 18 | CA/CAplus patent coverage enhanced |
| NEWS 29 | JUL 26 | USPATFULL/USPAT2 enhanced with IPC reclassification |
| NEWS 30 | JUL 30 | USGENE now available on STN |

NEWS EXPRESS 29 JUNE 2007: CURRENT WINDOWS VERSION IS V8.2,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

| | |
|---|---|
| NEWS HOURS | STN Operating Hours Plus Help Desk Availability |
| NEWS LOGIN | Welcome Banner and News Items |
| NEWS IPC8 | For general information regarding STN implementation of IPC 8 |

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 20:33:45 ON 31 JUL 2007

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files.  For example, the EXPAND
command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 20:34:10 ON 31 JUL 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   30 JUL 2007  HIGHEST RN 943719-65-1
DICTIONARY FILE UPDATES:  30 JUL 2007  HIGHEST RN 943719-65-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Documents and Settings\ahughes\My Documents\10587866.str

L1      STRUCTURE UPLOADED

=> s l1 sss sam
SAMPLE SEARCH INITIATED 20:34:54 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        1 TO ITERATE

100.0% PROCESSED         1 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            1 TO       80
```

```
PROJECTED ANSWERS:                0 TO        0

L2             0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 20:35:00 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -        59 TO ITERATE

100.0% PROCESSED       59 ITERATIONS                                  0 ANSWERS
SEARCH TIME: 00.00.01

L3             0 SEA SSS FUL L1

=> s caplus
L4             0 CAPLUS

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   178.40     178.61

FILE 'CAPLUS' ENTERED AT 20:36:17 ON 31 JUL 2007
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FILE COVERS 1907 - 31 Jul 2007  VOL 147 ISS 6
FILE LAST UPDATED: 30 Jul 2007  (20070730/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> s bisphosphonic acid
           489 BISPHOSPHONIC
       4409809 ACID
L5          402 BISPHOSPHONIC ACID
                (BISPHOSPHONIC(W)ACID)

=> s minodronate
L6           31 MINODRONATE

=> s minodronic acid hydrate
            40 MINODRONIC
       4409809 ACID
         86844 HYDRATE
L7            2 MINODRONIC ACID HYDRATE
                (MINODRONIC(W)ACID(W)HYDRATE)

=> s ym 529
          2621 YM
          4101 529
```

```
L8          13 YM 529
                (YM(W)529)

=> s yh529
L9          13 YH529

=> s yh 529
          1575 YH
          4101 529
L10         10 YH 529
                (YH(W)529)

=> s yh-529
          1575 YH
          4101 529
L11         10 YH-529
                (YH(W)529)

=> s ym-529
          2621 YM
          4101 529
L12         13 YM-529
                (YM(W)529)

=> s ym529
L13         25 YM529

=> s l13 and l12
L14          2 L13 AND L12

=> s l13 or l12 or l11 or l10 or l9 or l8 or l7 or l6
L15         84 L13 OR L12 OR L11 OR L10 OR L9 OR L8 OR L7 OR L6

=> s p2x2/3
'3' IS NOT A VALID FIELD CODE
L16          0 P2X2/3

=> s p2x
L17       2485 P2X

=> s p2x3
L18        537 P2X3

=> s l18 and l15
L19          1 L18 AND L15

=> d ibib hitstr abs l19

L19  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2005:729541  CAPLUS
DOCUMENT NUMBER:          143:166696
TITLE:                    P2X receptor inhibitor
INVENTOR(S):              Kakimoto, Shuichiro; Tamura, Seiji; Nagakura, Yukinori
PATENT ASSIGNEE(S):       Astellas Pharma Inc., Japan
SOURCE:                   PCT Int. Appl., 17 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     --------------       ----   --------    --------------------    --------
     WO 2005072746         A1    20050811    WO 2005-JP1067          20050127
```

```
        W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
            CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
            GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
            LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
            NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
            TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
        RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
            AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
            EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
            RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
            MR, NE, SN, TD, TG
    CA 2554749          A1    20050811    CA 2005-2554749        20050127
    EP 1709968          A1    20061011    EP 2005-704173         20050127
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS
PRIORITY APPLN. INFO.:                      JP 2004-24118       A  20040130
                                            WO 2005-JP1067      W  20050127
AB  As the results of intensive studies of searching for a compound of a novel
    type inhibiting P2X2/3,3 receptors, it is found out that minodronic acid,
    which is one of bisphosphonates having an effect of regulating bone
    resorption, has a favorable effect of inhibiting the P2X2/3,3 receptors
    and is usable as a preventive or a remedy for various pains.  Namely, a
    P2X2/3,3 receptor inhibitor, in particular, an analgesic which contains
    minodronic acid or its salt as the active ingredient.  The above-described
    "P2X2/3 and/or P2X3 receptor inhibitor" inhibits the functions
    of P2X2/3,3 receptors which are known as mols. participating in various
    pains such as nociceptive pain, inflammatory pain and neurogenic pain.
    Owing to this effect, it is useful in preventing or treating various pains
    wherein the P2X2/3,3 receptors participate in pain transmission.
REFERENCE COUNT:          24    THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> s l15 and l5
L20           4 L15 AND L5

=> s l15 or l5
L21         482 L15 OR L5

=> s l21 and l18
L22           1 L21 AND L18

=> d ibib hitstr abs l22

L22  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2005:729541  CAPLUS
DOCUMENT NUMBER:          143:166696
TITLE:                    P2X receptor inhibitor
INVENTOR(S):              Kakimoto, Shuichiro; Tamura, Seiji; Nagakura, Yukinori
PATENT ASSIGNEE(S):       Astellas Pharma Inc., Japan
SOURCE:                   PCT Int. Appl., 17 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2005072746         A1    20050811    WO 2005-JP1067          20050127
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
```

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            NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
            TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
        RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
            AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
            EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
            RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
            MR, NE, SN, TD, TG
    CA 2554749          A1    20050811    CA 2005-2554749        20050127
    EP 1709968          A1    20061011    EP 2005-704173         20050127
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS
PRIORITY APPLN. INFO.:                      JP 2004-24118       A  20040130
                                            WO 2005-JP1067      W  20050127
AB  As the results of intensive studies of searching for a compound of a novel
    type inhibiting P2X2/3,3 receptors, it is found out that minodronic acid,
    which is one of bisphosphonates having an effect of regulating bone
    resorption, has a favorable effect of inhibiting the P2X2/3,3 receptors
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    of P2X2/3,3 receptors which are known as mols. participating in various
    pains such as nociceptive pain, inflammatory pain and neurogenic pain.
    Owing to this effect, it is useful in preventing or treating various pains
    wherein the P2X2/3,3 receptors participate in pain transmission.
REFERENCE COUNT:         24    THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> s pantothenic acid
         7255 PANTOTHENIC
      4409809 ACID
L23      7151 PANTOTHENIC ACID
               (PANTOTHENIC(W)ACID)

=> s l23 and l18
L24           0 L23 AND L18

=> s l23 and l17
L25           0 L23 AND L17

=> s l5 and l17
L26           0 L5 AND L17

=> d his

     (FILE 'HOME' ENTERED AT 20:33:45 ON 31 JUL 2007)

     FILE 'REGISTRY' ENTERED AT 20:34:10 ON 31 JUL 2007
L1              STRUCTURE UPLOADED
L2            0 S L1 SSS SAM
L3            0 S L1 SSS FULL
L4            0 S CAPLUS

     FILE 'CAPLUS' ENTERED AT 20:36:17 ON 31 JUL 2007
L5          402 S BISPHOSPHONIC ACID
L6           31 S MINODRONATE
L7            2 S MINODRONIC ACID HYDRATE
L8           13 S YM 529
L9           13 S YH529
L10          10 S YH 529
L11          10 S YH-529
L12          13 S YM-529
L13          25 S YM529
```

| | | | |
|---|---|---|---|
| L14 | 2 | S | L13 AND L12 |
| L15 | 84 | S | L13 OR L12 OR L11 OR L10 OR L9 OR L8 OR L7 OR L6 |
| L16 | 0 | S | P2X2/3 |
| L17 | 2485 | S | P2X |
| L18 | 537 | S | P2X3 |
| L19 | 1 | S | L18 AND L15 |
| L20 | 4 | S | L15 AND L5 |
| L21 | 482 | S | L15 OR L5 |
| L22 | 1 | S | L21 AND L18 |
| L23 | 7151 | S | PANTOTHENIC ACID |
| L24 | 0 | S | L23 AND L18 |
| L25 | 0 | S | L23 AND L17 |
| L26 | 0 | S | L5 AND L17 |

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| NEWS | 25 | JUL 02 | CHEMCATS accession numbers revised |
| NEWS | 26 | JUL 02 | CA/CAplus enhanced with utility model patents from China |
| NEWS | 27 | JUL 16 | CAplus enhanced with French and German abstracts |
| NEWS | 28 | JUL 18 | CA/CAplus patent coverage enhanced |
| NEWS | 29 | JUL 26 | USPATFULL/USPAT2 enhanced with IPC reclassification |
| NEWS | 30 | JUL 30 | USGENE now available on STN |

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CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

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| NEWS LOGIN | Welcome Banner and News Items |
| NEWS IPC8 | For general information regarding STN implementation of IPC 8 |

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:53:27 ON 01 AUG 2007

=> file caplus
COST IN U.S. DOLLARS

| | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.21 | 0.21 |

FILE 'CAPLUS' ENTERED AT 14:53:37 ON 01 AUG 2007
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FILE COVERS 1907 - 1 Aug 2007 VOL 147 ISS 6
FILE LAST UPDATED: 31 Jul 2007 (20070731/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

```
=> s minodronic acid
            40 MINODRONIC
       4410376 ACID
L1          40 MINODRONIC ACID
               (MINODRONIC(W)ACID)

=> s minodronic
L2          40 MINODRONIC

=> s p2x2
L3         566 P2X2

=> s p2x3
L4         537 P2X3

=> s l4 and acid
       4410376 ACID
L5         121 L4 AND ACID

=> s acid or hydrate
       4410376 ACID
         86859 HYDRATE
L6     4473317 ACID OR HYDRATE

=> s l6 and l4
L7         124 L6 AND L4

=> s l7 and cancer
```

```
        323662 CANCER
L8           7 L7 AND CANCER

=> s l7 and bone
        208891 BONE
L9           5 L7 AND BONE

=> s nociceptive or inflammatory or neurogenic
          7997 NOCICEPTIVE
        183508 INFLAMMATORY
          6814 NEUROGENIC
L10     196165 NOCICEPTIVE OR INFLAMMATORY OR NEUROGENIC

=> s l7 and l10
L11          27 L7 AND L10

=> d ibib hitstr abs l11 1-27

L11  ANSWER 1 OF 27  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2007:703686  CAPLUS
DOCUMENT NUMBER:          147:118255
TITLE:                    Quinoline and quinazoline compositions and methods for
                          modulating gated ion channels and their preparation
INVENTOR(S):              Vohra, Rahul; Babinski, Kazimierz; Brochu, Jean-Louis;
                          Ntirampebura, Deogratias; Wei, Chang-Qing; Zamboni,
                          Robert Joseph
PATENT ASSIGNEE(S):       Painceptor Pharma Corporation, Can.
SOURCE:                   PCT Int. Appl., 155pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
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     WO 2007071055         A1    20070628    WO 2006-CA2105           20061221
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,
             KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK,
             MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
             RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.:                       US 2005-753201P     P  20051221
GI
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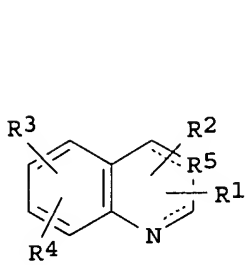
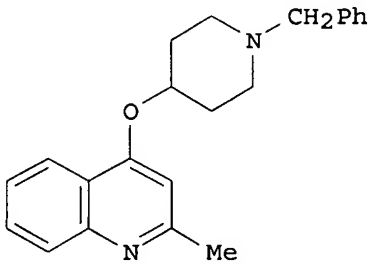



I




II

AB Disclosed are quinoline and quinazoline compds. of formula I, which modulate the activity of the gated ion channels compds. that modulate these gated ion channels are useful in the treatment of diseases and disorders related to pam, inflammation, the neurol. system, the gastrointestinal system and genitourinary system. The preferred compds. include quinoline or quinazoline derivs. substituted at the 4- position via N(H), C(O) or O moieties. Compds. of formula I wherein dashed line is single or double bond, wherein when the dashed lines is single bond, N of the ring may be bond to H and R1; R1, R3 and R4 are independently H, (un)substituted amine, CN, NO2, CO2H, and, halo, etc.; R2 is H, (un)substituted amino, amide, halo, NO2, (un)substituted aryl, etc.; R5 is N, C and CH; and their pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereoisomers, and racemates thereof, are claimed. Example compound II was prepared by substitution of 4-chloro-2-methylquinoline with 1-benzylpiperidin-4-ol. All the invention compds. were evaluated for their gated ion channel modulatory activity.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2007:592649 CAPLUS

DOCUMENT NUMBER: 147:88153

TITLE: Purinergic actions on neurons that modulate nociception in the rostral ventromedial medulla

AUTHOR(S): Selden, N. R.; Carlson, J. D.; Cetas, J.; Close, L. N.; Heinricher, M. M.

CORPORATE SOURCE: Department of Neurological Surgery, Oregon Health & Science University, Portland, OR, 97239, USA

SOURCE: Neuroscience (San Diego, CA, United States) (2007), 146(4), 1808-1816
CODEN: NRSCDN; ISSN: 0306-4522

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The rostral ventromedial medulla (RVM) serves as a critical link in bulbo-spinal nociceptive modulation. Within the RVM, off-cells' pause and on-cells' discharge immediately prior to a nocifensive reflex. These neurons are also activated and inactivated, resp., by local or systemic application of opioids. Off-cell activation leads to behavioral anti-nociception and on-cell activation to hyperalgesia. Thus, on- and off-cell populations allow bi-directional modulation of nociception by the RVM. A third neuronal population, neutral cells, shows no reflex-related change in discharge. The role of neutral cells in nociception, if any, is unknown. We investigated the responses of on-, off- and neutral cells to the iontophoretic application of purinergic ligands in lightly anesthetized rats. On-cell firing increased rapidly in response to application of ATP and to the P2X-receptor agonist, α,β-methylene ATP. Off-cell firing increased gradually in response to ATP and to the P2Y-receptor agonist, 2-methylthio-ATP. All of these responses were attenuated or reversed by the non-specific P2-receptor antagonists, suramin and pyridoxal-phosphate-6-azophenyl-2',4'-disulfonic acid (PPADS). Activation of off-cells was preferentially antagonized by the relatively selective P2Y antagonist, MRS2179. By contrast with activation of on- and off-cells by ATP, neutral cell firing was depressed by ATP, adenosine and the P1-receptor agonist, 5'-(N-ethylcarboxamido) adenosine (NECA). Neutral cell responses to these agonists were at least partially reversed by the adenosine-receptor antagonist, 8-phenyltheophylline (8PT). These data imply that on-cells preferentially express P2X-receptors, off-cells P2Y-receptors and neutral cells P1-receptors. Immunohistochem. localization of purinergic receptors confirms the presence of some subtypes of P2X, P2Y and A1 receptors on neuronal cell bodies and fibers within the RVM. The differential responses of on-, off- and neutral-cells to purinergic ligands highlight the value of pharmacol. signatures in

further delineation of the anatomy, connectivity and function of this therapeutically important system.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

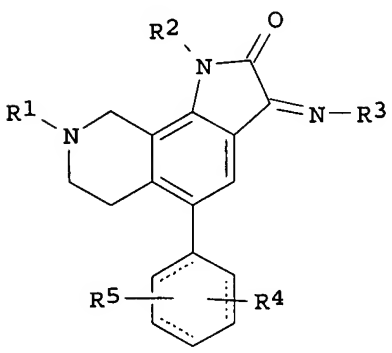
L11 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:590735 CAPLUS
DOCUMENT NUMBER: 147:30964
TITLE: Pyrroloisoquinolines and their preparation, compositions and methods for modulating gated ion channels
INVENTOR(S): Vohra, Rahul; Demnitz, Joachim; Ahring, Philip K.; Gan, Zhonghong; Gill, Nachhattarpal
PATENT ASSIGNEE(S): Painceptor Pharma Corporation, Can.
SOURCE: PCT Int. Appl., 118pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2007059608 | A1 | 20070531 | WO 2006-CA1897 | 20061122 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-739600P P 20051123
OTHER SOURCE(S): MARPAT 147:30964
GI

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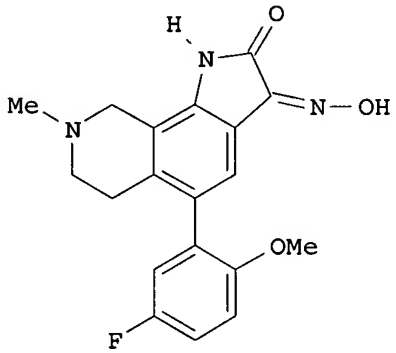



II

AB Pyrrolo-isoquinoline compds. according to formula I is disclosed. Compds. of formula I wherein dashed lines are single or double bonds; R1 is H, alkyl, alkoxy-alkyl, hydroxyalkyl, alkoxycarbonyl-alkyl, etc.; R2 is H, OH, alkyl, alkenyl, (CH2)1-4CO2H, CO-C1-4 alkyl, and SO2-C1-4 alkyl; R3 is H, OH, alkyl, acyl, benzyl, CO2H, CONMe2, OPh, OCF3, alkoxy, etc.; R4 and R5 are independently halo, CF3, NO2, NH2, CN, OH, alkoxy, PhO, Ph, SO2NH2 and derivs.; and their pharmaceutically acceptable salts, enantiomers,

stereoisomers, rotamers, tautomers, diastereoisomers, and racemates thereof, are claimed. These compds. and their pharmaceutical acceptable salts are used for modulating gated ion channels in order to treat pain, inflammatory disorders, neurol. disorders, or diseases associated with the genitourinary or gastrointestinal systems. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their ASIC antagonistic activity. From the assay, it was determined that compound II exhibited IC50 values of 0.10-0.20 μM.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN

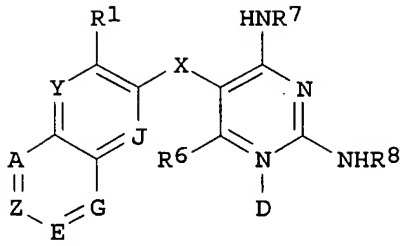
ACCESSION NUMBER: 2007:230748 CAPLUS
DOCUMENT NUMBER: 146:295953
TITLE: Preparation of diaminopyrimidines as P2X3 and P2X2/3 modulators
INVENTOR(S): Dillon, Michael Patrick; Jahangir, Alam; Lui, Alfred Sui-Ting; Wilhelm, Robert Stephen
PATENT ASSIGNEE(S): Roche Palo Alto LLC, USA
SOURCE: U.S. Pat. Appl. Publ., 32pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2007049610 | A1 | 20070301 | US 2006-510015 | 20060825 |
| WO 2007025900 | A1 | 20070308 | WO 2006-EP65525 | 20060821 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-713243P P 20050901
OTHER SOURCE(S): MARPAT 146:295953
GI



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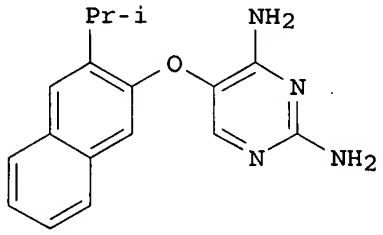


I

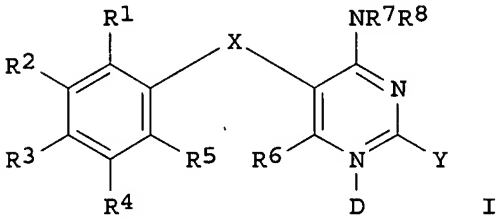
AB Title compds. I [X = CH2, O, S(O)n, NH, or N-alkyl; n = 0-2; D = optional O; one or two of A, E, G, J, Y and Z = N while the others are (un)substituted CH; or A, E, G, J, Y and Z = (un)substituted CH; R1 = alkenyl, alkynyl, halo, etc; R6 = H, halo, haloalkyl, aryl; R7-8 independently = H, alkoxyalkyl, heteroaryl, etc.], and their pharmaceutically acceptable salts, are prepared and disclosed for treating diseases mediated by a P2X3 and/or a P2X2/3 receptor antagonist. Thus, e.g., II was prepared by cyclocondensation of sodium nitromalonaldehyde (preparation given) with 3-methyl-2-pentanone followed by O-methylation, nitro reduction, and cyclocondensation with glycerol to provide 7-isopropyl-6-methoxyquinoline which is carried on in multiple steps to provide II. In FLIPR assays, II exhibited pIC50 of approx. 7.42 for the P2X3 receptor, and approx. 7.30 for the P2X2/3 receptor. Formulation examples are provided.

L11 ANSWER 5 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:230243 CAPLUS
DOCUMENT NUMBER: 146:295950
TITLE: Preparation of diaminopyrimidines as P2X3 and P2X2/3 antagonists for treatment of respiratory and gastrointestinal diseases
INVENTOR(S): Broka, Chris Allen; Carter, David Scott; Dillon, Michael Patrick; Ford, Anthony P. D. W.; Hawley, Ronald Charles; Jahangir, Alam; Moore, Amy Geraldine; Parish, Daniel Warren
PATENT ASSIGNEE(S): Roche Palo Alto LLC, USA
SOURCE: U.S. Pat. Appl. Publ., 133pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2007049609 | A1 | 20070301 | US 2006-509921 | 20060825 |
| WO 2007025925 | A1 | 20070308 | WO 2006-EP65606 | 20060823 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ,

UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: US 2005-713548P P 20050901
OTHER SOURCE(S): MARPAT 146:295950
GI

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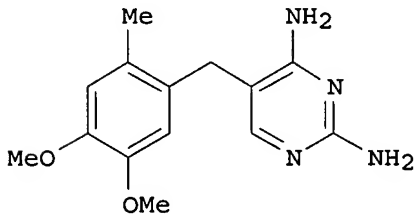



II

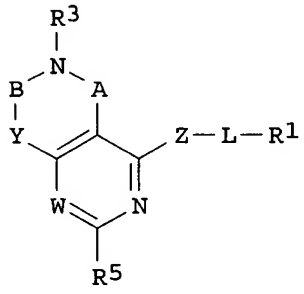
AB The invention is related to a method for treating a respiratory and gastrointestinal disease mediated by a P2X3 and P2X2/3 purinergic receptor antagonist by administering to a subject in need thereof an effective amount of diaminopyrimidine I [X = -CH2-, O, S(O)n, NH and derivs.; n = 0-2; Y = H, NH2 and derivs.; D = optional oxygen; R1 = alkyl, alkenyl, alkoxy, etc.; R2-5 = H, alkyl, alkenyl, amino, etc.; R6 = H, halo, amino, alkoxy, etc.; one of R7 and R8 = H and the other = H, cyclo/alkyl, acetyl, etc.] or a pharmaceutically acceptable salt thereof. Thus, e.g., II was prepared by condensation of 4,5-dimethoxy-2-methylbenzaldehyde with acrylonitrile followed by cyclocondensation with guanidine. Fluorimetric imaging assays were conducted to determine activity towards P2X3 receptor, e.g., 4-[(2,4-diaminopyrimidin-5-yl)oxy]-2-iodo-5-isopropylphenol demonstrated a pIC50 value of approx. 8.3. Formulation examples are also provided.

L11 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1176944 CAPLUS
DOCUMENT NUMBER: 145:489262
TITLE: Preparation of fused heterocyclic compounds for preventing and treating various diseases
INVENTOR(S): Kelly, Michael G.; Kincaid, John; Kaub, Carl J.
PATENT ASSIGNEE(S): Renovis, Inc., USA
SOURCE: PCT Int. Appl., 119pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| WO 2006119504 | A2 | 20061109 | WO 2006-US17614 | | 20060504 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| US 2006258689 | A1 | 20061116 | US 2006-429026 | | 20060504 |
| PRIORITY APPLN. INFO.: | | | US 2005-677760P | P | 20050504 |
| OTHER SOURCE(S): | MARPAT 145:489262 | | | | |

GI

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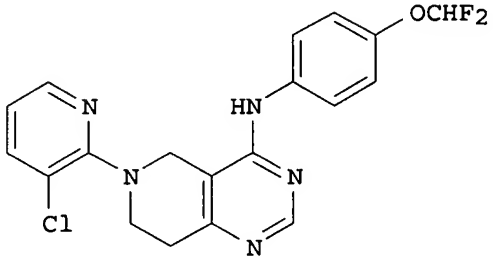



II

AB The title compds. I [A, B = (un)substituted CH2, CO or CS; Y = (un)substituted CH2; W = CR4, N; Z = O, NR2; L = (hetero)alkylene; R1 = carbocyclyl or heterocyclyl; R2 = H, alkyl, cycloalkyl; R3 = carbocyclyl or heterocyclyl; R4 = H, alkyl, acyl, etc.; R5 = R4, Z'-L'-R4 (wherein Z' = a bond, O, S, etc.; L' = alkylene)], useful for the prevention and treatment of a variety of conditions in mammals including humans, including by way of non-limiting example, pain, inflammation, cognitive disorders, anxiety, depression, and others, were prepared and formulated. E.g., a multi-step synthesis of II, starting from Et 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride, was given. The exemplified compds. I were tested in calcium uptake assay (P2X2 and P2X3) and % inhibition data were given for representative compds. I.

L11 ANSWER 7 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN

| | |
|---|---|
| ACCESSION NUMBER: | 2006:722186 CAPLUS |
| DOCUMENT NUMBER: | 145:224970 |
| TITLE: | P2X receptor ligands and pain |
| AUTHOR(S): | Shieh, Char-Chang; Jarvis, Michael F.; Lee, Chih-Hung; Perner, Richard J. |
| CORPORATE SOURCE: | Abbott Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL, 60064, USA |
| SOURCE: | Expert Opinion on Therapeutic Patents (2006), 16(8), 1113-1127<br>CODEN: EOTPEG; ISSN: 1354-3776 |
| PUBLISHER: | Informa Healthcare |
| DOCUMENT TYPE: | Journal; General Review |
| LANGUAGE: | English |

AB A review. P2X receptors belong to a superfamily of ligand-gated ion channels that conduct the influx of Ca2+, Na+ and K+ cations following activation by extracellular nucleotides such as ATP. Mol. cloning studies

have identified seven subunits, namely P2X1-7, that share .apprx. 40 - 50% identity in amino acid sequences within the subfamily. Using gene-silencing, pharmacol. and electrophysiol. approaches, recent studies have revealed roles for P2X2, P2X3, P2X4 and P2X7 receptors in nociceptive signaling. Homomeric P2X3 and heteromeric P2X2/3 receptors are highly localized in the peripheral sensory afferent neurons that conduct nociceptive sensory information to the spinal chord and brain. The discovery of A-317491, a selective and potent non-nucleotide P2X3 antagonist, provided a pharmacol. tool to determine the site and mode of action of P2X3-containing receptors in different pain behaviors, including neuropathic, inflammatory and visceral pain. Other P2X receptors (P2X4 and P2X7) that are predominantly expressed in microglia, macrophages and cells of immune origin can trigger the release of cytokines, such as IL-1-β and TNF-α. Genetic disruption of P2X4 and P2X7 signaling has been demonstrated to reduce inflammatory and neuropathic pain, suggesting that these two receptors might serve as integrators of neuroinflammation and pain. This article provides an overview of recent scientific literature and patents focusing on P2X3, P2X4 and P2X7 receptors, and the identification of small mol. ligands for the potential treatment of neuropathic and inflammatory pain.

REFERENCE COUNT: 113 THERE ARE 113 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:653836 CAPLUS

DOCUMENT NUMBER: 145:328730

TITLE: Inhibitory role of supraspinal P2X3/P2X2/3 subtypes on nociception in rats

AUTHOR(S): Fukui, Masato; Nakagawa, Takayuki; Minami, Masabumi; Satoh, Masamichi; Kaneko, Shuji

CORPORATE SOURCE: Department of Molecular Pharmacology, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, 606-8501, Japan

SOURCE: Molecular Pain (2006), 2, No pp. given
CODEN: MPOAC5; ISSN: 1744-8069
URL: http://www.molecularpain.com/content/pdf/1744-8069-2-19.pdf

PUBLISHER: BioMed Central Ltd.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Extracellular ATP is known to mediate synaptic transmission as a neurotransmitter or a neuromodulator via ionotropic P2X and metabotropic P2Y receptors. Several lines of evidence have suggested that ATP facilitates pain transmission at peripheral and spinal sites via the P2X receptors, in which the P2X3 subtype is considered as an important candidate for the effect. Conversely, we previously found that the activation of supraspinal P2X receptors evoked antinociception. However, the subtypes responsible for the antinociception via supraspinal P2X receptors remain unclear. In the present study, we showed that intracerebroventricular (i.c.v.) pretreatment with A-317491 (1 nmol), the novel non-nucleotide antagonist selective for P2X3 and P2X2/3 receptors, attenuated the antinociceptive effect produced by i.c.v. administered α,β-methylene-ATP (10 nmol), the P2X receptor agonist, in rats. Similarly, the abolishment of the P2X3 receptor mRNA in the brainstem by repeated i.c.v. pretreatments with antisense oligodeoxynucleotide for P2X3 gene once a day for 5 consecutive days diminished the antinociceptive effect of α,β-methylene-ATP. Furthermore, i.c.v. administration of A-317491 (1 and 10 nmol) significantly enhanced the inflammatory nociceptive behaviors induced by the intraplantar injection of formalin and i.p. injection of acetic acid. Taken together, these results suggest that supraspinal P2X3/P2X2/3 receptors

play an inhibitory role in pain transmission.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:446482 CAPLUS
DOCUMENT NUMBER: 145:181230
TITLE: The purinergic component of human vas deferens contraction
AUTHOR(S): Banks, Frederick C. L.; Knight, Gillian E.; Calvert, Robert C.; Thompson, Cecil S.; Morgan, Robert J.; Burnstock, Geoffrey
CORPORATE SOURCE: Royal Free and University College Medical School, London, UK
SOURCE: Fertility and Sterility (2006), 85(4), 932-939
CODEN: FESTAS; ISSN: 0015-0282
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To examine purinergic signaling in human vas deferens. Design: To study contractile responses of the scrotal vas deferens. Setting: Research department of a university teaching hospital. Patient(s): Undergoing vasectomy or orchidectomy (aged 27-88 years, n = 14). Intervention(s): Vasectomy or orchidectomy. Main Outcome Measure(s): Strips of vas deferens were suspended in an organ bath and subjected to elec. stimulation to establish frequency-response curves. These stimulations were repeated in the presence of pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid (PPADS, P2 receptor antagonist), prazosin (adrenergic α1 antagonist), and tetrodotoxin. Concentration-response curves were constructed to noradrenaline and the P2X agonists ATP and α,β-methylene ATP (α,β-meATP). The P2X receptor subtype distribution was assessed by immunohistochem. using specific antibodies. Result(s): The response at 32 Hz in the presence of PPADS was reduced by 40% and in the presence of prazosin by 80%. Noradrenaline caused concentration-dependent contractions (EC50 = 11.8 μM). Contractions to ATP and α,β-meATP (EC50 = 6.27 μM) suggested that the functional receptor was P2X1 and/or P2X3. However, immunohistochem. demonstrated P2X1, but not P2X3, receptor immunoreactivity on the smooth muscle cells. Conclusion(s): This study demonstrated that ATP is a co-transmitter with noradrenaline in the contraction of the human vas deferens predominantly acting through the P2X1 receptor.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:350899 CAPLUS
DOCUMENT NUMBER: 144:445564
TITLE: ATPγS enhances the production of inflammatory mediators by a human dermal endothelial cell line via purinergic receptor signaling
AUTHOR(S): Seiffert, Kristina; Ding, W.; Wagner, John A.; Granstein, Richard D.
CORPORATE SOURCE: Department of Dermatology, Weill Medical College of Cornell University, New York, NY, USA
SOURCE: Journal of Investigative Dermatology (2006), 126(5), 1017-1027
CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ATP affects multiple intra- and extracellular processes, including vascular tone and immune responses. Microvascular endothelial cells (EC)

play a central role in inflammation by recruitment of inflammatory cells from blood to tissues. We hypothesized that ATP (secreted by neurons and/or released after perturbation of cutaneous cells) may influence secretion of inflammatory messengers by dermal microvascular EC through actions on purinergic P2 receptors. Addition of the hydrolysis-resistant ATP analog, adenosine 5'-O-(3-thiotriphosphate) (ATPγS), to subconfluent cultures of the human microvascular endothelial cell-1 (HMEC-1) cell line led to a dose- and time-dependent increase in release of IL-6, IL-8, monocyte chemoattractant protein-1, and growth-regulated oncogene α. Both ATPγS-induced release and basal production of these proteins were significantly inhibited by the purinergic antagonists pyridoxal-5'-phosphate-6-azophenyl-2',5'-disulfonic acid (PPADS), pyridoxal-5'-phosphate-6(2'-naphthylazo-6-nitro-4',8'-disulfonate), and suramin. ATPγS increased expression of intercellular adhesion mol.-1 (ICAM-1), whereas suramin and PPADS decreased both ATPγS-induced and basal ICAM-1 expression. Using PCR, we found that HMEC-1 strongly express mRNA for the P2X4, P2X5, P2X7, P2Y2, and P2Y11 receptors and weakly express mRNA for P2X1 and P2X3 receptors. Purinergic nucleotides may mediate acute inflammation in the skin and thus contribute to physiol. and pathophysiol. inflammation. For example, ATP may contribute to both the vasodilation and the inflammation associated with Rosacea.

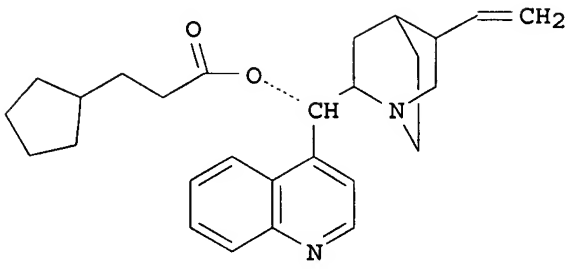
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:343936 CAPLUS
DOCUMENT NUMBER: 144:382035
TITLE: Compositions and therapeutic methods using cyclic and heterocyclic compound gated ion channel modulators
INVENTOR(S): Babinski, Kazimierz; Szarek, Walter A.; Vohra, Rahul; Varming, Thomas; Ahring, Philip K.; Dyhring Joergensen, Tino; Blackburn-Munro, Gordon John
PATENT ASSIGNEE(S): Painceptor Pharma Corp., Can.; Neurosearch A/S
SOURCE: PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2006038070 | A2 | 20060413 | WO 2005-IB2613 | | 20050330 |
| WO 2006038070 | A3 | 20060601 | | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| CA 2561993 | A1 | 20060413 | CA 2005-2561993 | | 20050330 |
| EP 1734962 | A2 | 20061227 | EP 2005-805035 | | 20050330 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU | | | | | |
| US 2007004680 | A1 | 20070104 | US 2005-96239 | | 20050330 |
| PRIORITY APPLN. INFO.: | | | US 2004-558059P | P | 20040330 |
| | | | US 2004-564063P | P | 20040420 |

WO 2005-IB2613 W 20050330

OTHER SOURCE(S): MARPAT 144:382035
GI



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AB The invention discloses compns. and therapeutic methods using cyclic and heterocyclic compound gated ion channel modulators. Tested compds. include e.g. I.

L11 ANSWER 12 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:213863 CAPLUS
DOCUMENT NUMBER: 144:429775
TITLE: ASIC3, an acid-sensing ion channel, is expressed in metaboreceptive sensory neurons
AUTHOR(S): Molliver, Derek C.; Immke, David C.; Fierro, Leonardo; Pare, Michel; Rice, Frank L.; McCleskey, Edwin W.
CORPORATE SOURCE: Vollum Institute, Oregon Health and Science University, Portland, OR, 97239, USA
SOURCE: Molecular Pain (2005), 1(Nov.), No pp. given
CODEN: MPOAC5; ISSN: 1744-8069
URL: http://www.molecularpain.com/content/pdf/1744-8069-1-35.pdf
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Background: ASIC3, the most sensitive of the acid-sensing ion channels, depolarizes certain rat sensory neurons when lactic acid appears in the extracellular medium. Two functions have been proposed for it: (1) ASIC3 might trigger ischemic pain in heart and muscle; (2) it might contribute to some forms of touch mechanosensation. Here, we used immunocytochem., retrograde labeling, and electrophysiol. to ask whether the distribution of ASIC3 in rat sensory neurons is consistent with either of these hypotheses. Results: Less than half (40%) of dorsal root ganglion sensory neurons react with anti-ASIC3, and the population is heterogeneous. They vary widely in cell diameter and express different growth factor receptors: 68% express TrkA, the receptor for nerve growth factor, and 25% express TrkC, the NT3 growth factor receptor. Consistent with a role in muscle nociception, small (<25 μm) sensory neurons that innervate muscle are more likely to express ASIC3 than those that innervate skin (51% of small muscle afferents vs. 28% of small skin afferents). Over 80% of ASIC3+ muscle afferents co-express CGRP (a vasodilatory peptide). Remarkably few (9%) ASIC3+ cells express P2X3 receptors (an ATP-gated ion channel), whereas 31% express TRPV1 (the noxious heat and capsaicin-activated ion channel also known as VR1). ASIC3+/CGRP+ sensory nerve endings were observed on muscle arterioles, the blood vessels that control vascular resistance; like the cell bodies, the endings are P2X3- and can be TRPV1+. The TrkC+/ASIC3+ cell bodies are uniformly large, possibly consistent with non-nociceptive mechanosensation. They are not proprioceptors because they fail two other tests: ASIC3+ cells do not express parvalbumin and they are absent from the mesencephalic trigeminal nucleus. Conclusion: Our data indicates that: (1) ASIC3 is expressed in a restricted population

of nociceptors and probably in some non-nociceptors; (2) co-expression of ASIC3 and CGRP, and the absence of P2X3, are distinguishing properties of a class of sensory neurons, some of which innervate blood vessels. We suggest that these latter afferents may be muscle metaboreceptors, neurons that sense the metabolic state of muscle and can trigger pain when there is insufficient oxygen.
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 13 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:213839 CAPLUS
DOCUMENT NUMBER: 144:448347
TITLE: Contrasting phenotypes of putative proprioceptive and nociceptive trigeminal neurons innervating jaw muscle in rat
AUTHOR(S): Connor, Mark; Naves, Ligia A.; McCleskey, Edwin W.
CORPORATE SOURCE: Vollum Institute, Oregon Health and Sciences University, Portland, OR, USA
SOURCE: Molecular Pain (2005), 1(Oct.), No pp. given
CODEN: MPOAC5; ISSN: 1744-8069
URL: http://www.molecularpain.com/content/pdf/1744-8069-1-31.pdf
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Background: Despite the clin. significance of muscle pain, and the extensive investigation of the properties of muscle afferent fibers, there has been little study of the ion channels on sensory neurons that innervate muscle. In this study, we have fluorescently tagged sensory neurons that innervate the masseter muscle, which is unique because cell bodies for its muscle spindles are in a brainstem nucleus (mesencephalic nucleus of the 5th cranial nerve, MeV) while all its other sensory afferents are in the trigeminal ganglion (TG). We examine the hypothesis that certain mols. proposed to be used selectively by nociceptors fail to express on muscle spindles afferents but appear on other afferents from the same muscle. Results: MeV muscle afferents perfectly fit expectations of cells with a non-nociceptive sensory modality: Opiates failed to inhibit calcium channel currents (ICa) in 90% of MeV neurons, although ICa were inhibited by GABAB receptor activation. All MeV afferents had brief (I msec) action potentials driven solely by tetrodotoxin (TTX)-sensitive Na channels and no MeV afferent expressed either of three ion channels (TRPVI, P2X3, and ASIC3) thought to be transducers for nociceptive stimuli, although they did express other ATP and acid-sensing channels. Trigeminal masseter afferents were much more diverse. Virtually all of them expressed at least one, and often several, of the three putative nociceptive transducer channels, but the mix varied from cell to cell. Calcium currents in 80% of the neurons were measurably inhibited by μ-opioids, but the extent of inhibition varied greatly. Almost all TG masseter afferents expressed some TTX-insensitive sodium currents, but the amount compared to TTX sensitive sodium current varied, as did the duration of action potentials. Conclusion: Most masseter muscle afferents that are not muscle spindle afferents express mols. that are considered characteristic of nociceptors, but these putative muscle nociceptors are molecularly diverse. This heterogeneity may reflect the mixture of metabosensitive afferents which can also signal noxious stimuli and purely nociceptive afferents characteristic of muscle.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 14 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:163185 CAPLUS
DOCUMENT NUMBER: 144:347378
TITLE: Runx1 determines nociceptive sensory neuron

phenotype and is required for thermal and neuropathic pain

AUTHOR(S): Chen, Chih-Li; Broom, Daniel C.; Liu, Yang; de Nooij, Joriene C.; Li, Zhe; Cen, Chuan; Abdel Samad, Omar; Jessell, Thomas M.; Woolf, Clifford J.; Ma, Qiufu

CORPORATE SOURCE: Dana-Farber Cancer Institute and Department of Neurobiology, Harvard Medical School, Boston, MA, 02115, USA

SOURCE: Neuron (2006), 49(3), 365-377
CODEN: NERNET; ISSN: 0896-6273

PUBLISHER: Cell Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In mammals, the perception of pain is initiated by the transduction of noxious stimuli through specialized ion channels and receptors expressed by nociceptive sensory neurons. The mol. mechanisms responsible for the specification of distinct sensory modality are, however, largely unknown. We show here that Runx1, a Runt domain transcription factor, is expressed in most nociceptors during embryonic development but in adult mice, becomes restricted to nociceptors marked by expression of the neurotrophin receptor Ret. In these neurons, Runx1 regulates the expression of many ion channels and receptors, including TRP class thermal receptors, Na+-gated, ATP-gated, and H+-gated channels, the opioid receptor MOR, and Mrgpr class G protein coupled receptors. Runx1 also controls the lamina-specific innervation pattern of nociceptive afferents in the spinal cord. Moreover, mice lacking Runx1 exhibit specific defects in thermal and neuropathic pain. Thus, Runx1 coordinates the phenotype of a large cohort of nociceptors, a finding with implications for pain therapy.

REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 15 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:23513 CAPLUS

DOCUMENT NUMBER: 144:80426

TITLE: Are tender point injections beneficial: The role of tonic nociception in fibromyalgia

AUTHOR(S): Staud, Roland

CORPORATE SOURCE: Division of Rheumatology and Clinical Immunology, University of Florida, Gainesville, FL, 32610-0221, USA

SOURCE: Current Pharmaceutical Design (2006), 12(1), 23-27
CODEN: CPDEFP; ISSN: 1381-6128

PUBLISHER: Bentham Science Publishers Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Characteristic symptoms of fibromyalgia syndrome (FM) include widespread pain, fatigue, sleep abnormalities, and distress. FM patients show psychophys. evidence for mech., thermal, and elec. hyperalgesia. To fulfill FM criteria, the mech. hyperalgesia needs to be widespread and present in at least 11 out of 18 well-defined body areas (tender points). Peripheral and central abnormalities of nociception have been described in FM and these changes may be relevant for the increased pain experienced by these patients. Important nociceptor systems in the skin and muscle seem to undergo profound changes in FM patients by yet unknown mechanisms. These changes may result from the release of algesic substances after muscle or other soft tissue injury. These pain mediators can sensitize important nociceptor systems, including the transient receptor potential channel, vanilloid subfamily member 1 (TRPV1), acid sensing ion channel (ASIC) receptors, and purino-receptors (P2X3). Subsequently, tissue mediators of inflammation and nerve growth factors can excite these receptors and cause substantial changes in pain sensitivity. FM pain is widespread and does not seem to be restricted to tender points (TP). It frequently comprises multiple areas of deep tissue

pain (trigger points) with adjacent much larger areas of referred pain. Analgesia of areas of extensive nociceptive input has been found to provide often long lasting local as well as general pain relief. Thus interventions aimed at reducing local FM pain seem to be effective but need to focus less on tender points but more on trigger points (TrP) and other body areas of heightened pain and inflammation.

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 16 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1029416 CAPLUS
DOCUMENT NUMBER: 144:122114
TITLE: Endogenous ATP involvement in mustard-oil-induced central sensitization in trigeminal subnucleus caudalis (medullary dorsal horn)
AUTHOR(S): Chiang, C. Y.; Zhang, S.; Xie, Y. F.; Hu, J. W.; Dostrovsky, J. O.; Salter, M. W.; Sessle, B. J.
CORPORATE SOURCE: Faculty of Dentistry, The Hospital of Sick Children, University of Toronto, Toronto, ON, Can.
SOURCE: Journal of Neurophysiology (2005), 94(3), 1751-1760
CODEN: JONEA4; ISSN: 0022-3077
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Central sensitization represents a sustained hypersensitive state of dorsal horn nociceptive neurons that can be evoked by peripheral inflammation or injury to nerves and tissues. It reflects neuroplastic changes such as increases in neuronal spontaneous activity, receptive field size, and responses to suprathreshold stimuli and a decrease in activation threshold. We recently demonstrated that purinergic receptor mechanisms in trigeminal subnucleus caudalis (Vc; medullary dorsal horn) are also involved in the initiation and maintenance of central sensitization in brain stem nociceptive neurons of trigeminal subnucleus oralis. The aim of the present study was to investigate whether endogenous ATP is involved in the development of central sensitization in Vc itself. The expts. were carried out on urethane/α-chloralose anesthetized and immobilized rats. Single neurons were recorded and identified as nociceptive-specific (NS) in the deep laminae of Vc. During continuous saline superfusion (0.6 mL/h it) over the caudal medulla, Vc neuronal central sensitization was readily induced by mustard oil application to the tooth pulp. However, this mustard-oil-induced central sensitization could be completely blocked by continuous intrathecal superfusion of the wide-spectrum P2X receptor antagonist pyridoxal-phosphate-6-azophenyl-2, 4-disulfonic acid tetra-sodium (33-100 μM) and by apyrase (an ectonucleotidase enzyme, 30 units/mL). Superfusion of the selective P2X1, P2X3 and P2X2/3 receptor antagonist 2',3'-O-(2,4,6-trinitrophenyl) ATP (6-638 μM) partially blocked the Vc central sensitization. The two P2X receptor antagonists did not significantly affect the baseline nociceptive properties of the Vc neurons. These findings implicate endogenous ATP as an important mediator contributing to the development of central sensitization in nociceptive neurons of the deep laminae of the dorsal horn.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 17 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:729541 CAPLUS
DOCUMENT NUMBER: 143:166696
TITLE: P2X receptor inhibitor
INVENTOR(S): Kakimoto, Shuichiro; Tamura, Seiji; Nagakura, Yukinori
PATENT ASSIGNEE(S): Astellas Pharma Inc., Japan
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005072746 | A1 | 20050811 | WO 2005-JP1067 | 20050127 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2554749 | A1 | 20050811 | CA 2005-2554749 | 20050127 |
| EP 1709968 | A1 | 20061011 | EP 2005-704173 | 20050127 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS | | | | |

PRIORITY APPLN. INFO.: JP 2004-24118 A 20040130
WO 2005-JP1067 W 20050127

AB As the results of intensive studies of searching for a compound of a novel type inhibiting P2X2/3,3 receptors, it is found out that minodronic acid, which is one of bisphosphonates having an effect of regulating bone resorption, has a favorable effect of inhibiting the P2X2/3,3 receptors and is usable as a preventive or a remedy for various pains. Namely, a P2X2/3,3 receptor inhibitor, in particular, an analgesic which contains minodronic acid or its salt as the active ingredient. The above-described "P2X2/3 and/or P2X3 receptor inhibitor" inhibits the functions of P2X2/3,3 receptors which are known as mols. participating in various pains such as nociceptive pain, inflammatory pain and neurogenic pain. Owing to this effect, it is useful in preventing or treating various pains wherein the P2X2/3,3 receptors participate in pain transmission.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 18 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:892418 CAPLUS
DOCUMENT NUMBER: 141:360591
TITLE: A-317491, a selective P2X3/P2X2/3 receptor antagonist, reverses inflammatory mechanical hyperalgesia through action at peripheral receptors in rats
AUTHOR(S): Wu, Gang; Whiteside, Garth T.; Lee, Gary; Nolan, Scott; Niosi, Mark; Pearson, Michelle S.; Ilyin, Victor I.
CORPORATE SOURCE: Purdue Pharma Discovery Research, Cranbury, NJ, 08512, USA
SOURCE: European Journal of Pharmacology (2004), 504(1-2), 45-53
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of A-317491 (5-({(3-Phenoxybenzyl)[(1S)-1,2,3,4-tetrahydro-1-naphthalenyl]amino}carbonyl)-1,2,4-benzenetricarboxylic acid), a recently described selective P2X3 and P2X2/3 receptor antagonist, on inflammatory mech. hyperalgesia was examined In the rat Freund's complete adjuvant model of inflammatory pain,

s.c. administration of A-317491 dose-dependently reversed mech. hyperalgesia. Maximum percent reversal (72%) was seen 3 h after administration at 10 mg/kg. Substantial plasma concns. were measured for A-317491 after s.c. dosing 3, 10 and 30 mg/kg. However, the brain-to-plasma concentration ratio, determined 1 h after a 10 mg/kg s.c. dose, indicated limited penetration of A-317491 into the central nervous system. As revealed by neural activity recorded from single C-fiber nociceptive afferent in a Freund's complete adjuvant-inflamed rat skin-nerve preparation, topical application of A-317491 completely blocked afferent activation and mech. sensitization induced by α,β-methylene ATP, a P2X agonist. These results suggest that A-317491 is a peripherally acting P2X blocker. Its efficacy demonstrates the importance of peripheral P2X3/P2X2/3 receptors in mediating ATP-associated mech. hyperalgesia following inflammation, confirming previous suggestions of a significant role for P2X2/3.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 19 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:213046 CAPLUS

DOCUMENT NUMBER: 141:52081

TITLE: Contribution of sensitized P2X receptors in inflamed tissue to the mechanical hypersensitivity revealed by phosphorylated ERK in DRG neurons

AUTHOR(S): Dai, Yi; Fukuoka, Tetsuo; Wang, Hu; Yamanaka, Hiroki; Obata, Koichi; Tokunaga, Atsushi; Noguchi, Koichi

CORPORATE SOURCE: Department of Anatomy and Neuroscience, Hyogo College of Medicine, Hyogo, 663-8501, Japan

SOURCE: Pain (2004), 108(3), 258-266
CODEN: PAINDB; ISSN: 0304-3959

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The mechanism of mech. hyperalgesia in inflammation might involve a mechanochem.' process whereby stretch evokes the release of ATP from the damaged tissue that then excites nearby primary sensory nerve terminals. In the present study, phosphorylated extracellular signal-regulated protein kinase (pERK) immunoreactivity was used as a marker indicating functional activation of primary afferent neurons to examine the P2X receptor-mediated noxious response in DRG neurons in a rat model of peripheral inflammation. We found that very few pERK-labeled DRG neurons were detected in normal rats after alpha, beta methylene-ATP (αβme-ATP) intraplantar injection. However, a number of DRG neurons were labeled for pERK after αβme-ATP injection to the complete Freund's adjuvant (CFA) induced inflamed paw. Seventy-three percent of pERK-labeled DRG neurons co-expressed the P2X3 receptor. After mech. noxious stimulation to the hind paw of CFA-inflamed rats, we found many more pERK-labeled neurons compared to those in the normal rats. Administration of the P2X3 receptor antagonists, pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid or 2'- (or 3')-O-(trinitrophenyl)ATP (TNP-ATP), significantly decreased the mech. stimulation-evoked pERK labeling in CFA-inflamed rats, but not in normal rats. We also found the recruitment of neurons with myelinated A fibers labeled for pERK in CFA-inflamed rats, which was reversed by P2X3 receptor antagonists. Moreover, TNP-ATP dose dependently reduced the mech. hypersensitivity of CFA rats. These data suggest that the P2X receptors in primary afferent neurons increase their activity with enhanced sensitivity of the intracellular ERK signaling pathway during inflammation and then contribute to the hypersensitivity to mech. noxious stimulation in the inflammatory state.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 20 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:157136 CAPLUS
DOCUMENT NUMBER: 140:332893
TITLE: Inhibition of N-type voltage-activated calcium channels in rat dorsal root ganglion neurons by P2Y receptors is a possible mechanism of ADP-induced analgesia
AUTHOR(S): Gerevich, Zoltan; Borvendeg, Sebestyen J.; Schroeder, Wolfgang; Franke, Heike; Wirkner, Kerstin; Noerenberg, Wolfgang; Fuerst, Susanna; Gillen, Clemens; Illes, Peter
CORPORATE SOURCE: Rudolf-Boehm-Institute of Pharmacology and Toxicology, University of Leipzig, Leipzig, D-04107, Germany
SOURCE: Journal of Neuroscience (2004), 24(4), 797-807
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Patch-clamp recordings from small-diameter rat dorsal root ganglion (DRG) neurons maintained in culture demonstrated preferential inhibition by ATP of high-voltage-activated, but not low-voltage-activated, Ca2+ currents (ICa). The rank order of agonist potency was UTP > ADP > ATP. ATP depressed the ω-conotoxin GVIA-sensitive N-type current only. Pyridoxal-5-phosphate-6-azophenyl-2',4'-disulfonic acid (PPADS) and 2'-deoxy-N6-methyladenosine 3',5'-bisphosphate tetraammonium, two P2Y1 receptor antagonists, almost abolished the ATP-induced inhibition. Both patch-clamp recordings and immunocytochem. coupled with confocal laser microscopy indicated a colocalization of functional P2X3 and P2Y1 receptors on the same DRG neurons. Because the effect of ATP was inhibited by intracellular guanosine 5'-O-(2-thiodiphosphate) or by applying a strongly depolarizing prepulse, P2Y1 receptors appear to block ICa by a pathway involving the βγ subunit of a Gq/11 protein. Less efficient buffering of the intracellular Ca2+ concentration ([Ca2+]i) by reducing the intrapipette EGTA failed to interfere with the ATP effect. Fura-2 microfluorimetry suggested that ATP raised [Ca2+]i by a Gα-mediated release from intracellular pools and simultaneously depressed the high external potassium concentration-induced increase of [Ca2+]i by inhibiting ICa via Gβγ. Adenosine 5'-O-(2-thiodiphosphate) inhibited dorsal root-evoked polysynaptic population EPSPs in the semisected rat spinal cord and prolonged the nociceptive threshold on intrathecal application in the tail-flick assay. These effects were not antagonized by PPADS. Hence, P2Y receptor activation by ADP, which is generated by enzymic degradation of ATP, may decrease the release of glutamate from DRG terminals in the spinal cord and thereby partly counterbalance the allogenic effect of ATP.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 21 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:978893 CAPLUS
DOCUMENT NUMBER: 140:193632
TITLE: Purinergic mechanisms contribute to mechanosensory transduction in the rat colorectum
AUTHOR(S): Wynn, Gregory; Rong, Weifang; Xiang, Zhenghua; Burnstock, Geoffrey
CORPORATE SOURCE: Automic Neuroscience Institute, Royal Free and University College Medical School, London, UK
SOURCE: Gastroenterology (2003), 125(5), 1398-1409
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background & Aims: ATP plays a role in peripheral sensory mechanisms and, in particular, mechanosensory transduction in the urinary system. P2X3 receptors are selectively expressed on small-diameter sensory

neurons in the dorsal root ganglia; sensory neurons from dorsal root ganglia L1 and S1 supply the colorectum. This study investigated whether purinergic signaling contributes to mechanosensory transduction in the rat colorectum. Methods: A novel in vitro rat colorectal preparation was used to elucidate whether ATP is released from the mucosa in response to distention and to evaluate whether it contributes to sensory nerve discharge during distention. Results: P2X3 receptor immunostaining was present on subpopulations of neurons in L1 and S1 dorsal root ganglia, which supply the rat colorectum. Distention of the colorectum led to pressure-dependent increases in ATP release from colorectal epithelial cells and also evoked pelvic nerve excitation, which was mimicked by application of ATP and α,β-methylene ATP. The sensory nerve discharges evoked by distention were potentiated by α,β-methylene ATP and ARL-67156, an ATPase inhibitor, and were attenuated by the selective P2X1, P2X3, and P2X2/3 antagonist 2',3'-O-trinitrophenyladenosine 5'-triphosphate and by the nonselective P2 antagonists pyridoxyl 5-phosphate 6-azophenyl-2',4'-disulfonic acid and suramin. Adenosine, after ectoenzymic breakdown of ATP, seems to be involved in the longer-lasting distention-evoked sensory discharge. Single-fiber anal. showed that high-threshold fibers were particularly affected by α,β-methylene ATP, suggesting a correlation between purinergic activation and nociceptive stimuli. Conclusions: ATP contributes to mechanosensory transduction in the rat colorectum, and this is probably associated with pain.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 22 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:825391 CAPLUS
DOCUMENT NUMBER: 138:66758
TITLE: Molecular physiology of P2X receptors
AUTHOR(S): North, R. Alan
CORPORATE SOURCE: Institute of Molecular Physiology, University of Sheffield, Sheffield, UK
SOURCE: Physiological Reviews (2002), 82(4), 1013-1067
CODEN: PHREA7; ISSN: 0031-9333
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. P2X receptors are membrane ion channels that open in response to the binding of extracellular ATP. Seven genes in vertebrates encode P2X receptor subunits, which are 40-50% identical in amino acid sequence. Each subunit has two transmembrane domains, separated by an extracellular domain (.apprx.280 amino acids). Channels form as multimers of several subunits. Homomeric P2X1, P2X2, P2X3, P2X4, P2X5, and P2X7 channels and heteromeric P2X2/3 and P2X1/5 channels have been most fully characterized following heterologous expression. Some agonists (e.g., αβ-methylene ATP) and antagonists [e.g., 2',3'-O-(2,4,6-trinitrophenyl)-ATP] are strongly selective for receptors containing P2X1 and P2X3 subunits. All P2X receptors are permeable to small monovalent cations; some have significant calcium or anion permeability. In many cells, activation of homomeric P2X7 receptors induces a permeability increase to larger organic cations including some fluorescent dyes and also signals to the cytoskeleton; these changes probably involve addnl. interacting proteins. P2X receptors are abundantly distributed, and functional responses are seen in neurons, glia, epithelia, endothelia, bone, muscle, and hemopoietic tissues. The mol. composition of native receptors is becoming understood, and some cells express more than one type of P2X receptor. On smooth muscles, P2X receptors respond to ATP released from sympathetic motor nerves (e.g., in ejaculation). On sensory nerves, they are involved in the initiation of afferent signals in several viscera (e.g., bladder, intestine) and play a key role in sensing tissue-damaging and inflammatory stimuli. Paracrine roles for ATP signaling through P2X receptors are likely in

neurohypophysis, ducted glands, airway epithelia, kidney, bone, and hemopoietic tissues. In the last case, P2X7 receptor activation stimulates cytokine release by engaging intracellular signaling pathways.

REFERENCE COUNT: 526 THERE ARE 526 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 23 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:249685 CAPLUS
DOCUMENT NUMBER: 138:49746
TITLE: TNP-ATP, a potent P2X3 receptor antagonist, blocks acetic acid-induced abdominal constriction in mice: comparison with reference analgesics
AUTHOR(S): Honore, Prisca; Mikusa, Joseph; Bianchi, Bruce; McDonald, Heath; Cartmell, Jayne; Faltynek, Connie; Jarvis, Michael F.
CORPORATE SOURCE: Neuroscience Research, Global Pharmaceutical Research and Development, Dept D04PM, Abbott Laboratories, Abbott Park, IL, 60064, USA
SOURCE: Pain (2002), 96(1-2), 99-105
CODEN: PAINDB; ISSN: 0304-3959
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Exogenous ATP has been shown to be allogenic in both animal and humans. Research has focused on the P2X3 ligand-gated ion channel, as it is preferentially expressed on nociceptive C-fibers. In addition, P2X3 receptor gene disrupted mice show decreased responses to somatic painful stimuli. However, the potential role of P2X receptor activation in visceral pain has not yet been evaluated. In the present study, the systemic administration of suramin, and pyridoxal-phosphate-6-azophenyl-2',4'-disulfonic acid, PPADS, both non-selective P2X receptor antagonists, dose-dependently reduced acetic acid -induced abdominal constrictions in mice (ED50=34.5 μmol/kg and ED50=70 μmol/kg, resp.). Furthermore, 2'-(or-3')-O-(trinitrophenyl)adenosine 5'- tri-phosphate (TNP-ATP) potently (IC50=10 nM) blocked the functional activation of P2X3 receptors in vitro and attenuated acetic acid-induced visceral pain. In the abdominal constriction assay, TNP-ATP (ED50=6.35 μmol/kg, i.p.) was 6-10 fold more potent than suramin and PPADS to reduce nociceptive behavior. In addition, TNP-ATP was 10 fold more potent than TNP-AMP (2'-(or-3')-O-(trinitrophenyl)adenosine 5'-mono-phosphate) (ED50=63.5 μmol/kg, i.p.) at reducing acetic acid-induced nociception. At the highest dose, TNP-ATP completely abolished nociceptive behavior, as did morphine (ED50=3 μmol/kg, i.p.). While TNP-ATP is also a potent antagonist of P2X1 receptors, P2X1 receptor mediated responses have not been shown in dorsal root ganglia and diinosine pentaphosphate, IP5I, a potent and selective P2X1 receptor antagonist, was ineffective at reducing abdominal constrictions. Thus, the antinociceptive effects of TNP-ATP appear to be mediated through activation of homomeric P2X3 and/or heteromeric P2X2/3 receptors. Together, these results show that activation of P2X3 containing receptors plays a role in the transmission of inflammatory visceral pain.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 24 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:756862 CAPLUS
DOCUMENT NUMBER: 133:317928
TITLE: Human purinoceptor P2X3 and its encoding cDNA, methods of altering P2X3 receptor activity and its therapeutic uses
INVENTOR(S): Jarvis, Michael F.; Lynch, Kevin J.; Burgard, Edward

C.; Vanbiesen, Timothy; Kowaluk, Elizabeth A.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000063379 | A2 | 20001026 | WO 2000-US10919 | 20000421 |
| WO 2000063379 | A3 | 20011115 | | |
| W: CA, JP, MX | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2370659 | A1 | 20001026 | CA 2000-2370659 | 20000421 |
| EP 1180141 | A2 | 20020220 | EP 2000-926289 | 20000421 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 2004500021 | T | 20040108 | JP 2000-612458 | 20000421 |
| MX 2001PA10646 | A | 20020506 | MX 2001-PA10646 | 20011019 |

PRIORITY APPLN. INFO.: US 1999-130339P P 19990421
WO 2000-US10919 W 20000421

AB The subject invention relates to the P2X3 receptor, methods of modulating the activity of the P2X3 receptor, and to uses of these methods. The predicted amino acid sequence of rat P2X3 purinoceptor was used to search for human DNA sequences which would code for similar polypeptides, and 5'- and 3'-RACE products of an EST (expressed sequence tag) in the public databases yielded a cDNA containing the intact open reading frame for human P2X3. The present invention also includes a method of potentiating the effects of an agonist which activates P2X3 comprising incubating cells with a triazene dye such as Cibacron Blue and exposing the incubated cell to an agonist. Cibacron Blue has the ability to mediate approx. a 3-7-fold increase in the magnitude and potency of ATP-activated Ca2+ influx and transmembrane currents associated with the P2X3 receptors. Inhibitory activity of a non-selective P2 receptor antagonist on a P2X3 receptor can be blocked by incubation of the cells with a triazene dye and exposing the incubated cells to a non-selective P2 receptor agonist. Nociceptive effects in a mammal can be inhibited by administering a P2X receptor antagonist such as PPADS (pyridoxal-5-phosphate-6-azophenyl-2',4'-disulfonic acid) or TNP-ATP (2' or 3'-O-(2,4,6-trinitrophenyl)-ATP). In particular, such methods may be used, for example, to accelerate the rate of resensitization of a desensitized receptor.

L11 ANSWER 25 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:810142 CAPLUS
DOCUMENT NUMBER: 132:117874
TITLE: Evidence for the involvement of spinal endogenous ATP and P2X receptors in nociceptive responses caused by formalin and capsaicin in mice
AUTHOR(S): Tsuda, Makoto; Ueno, Shinya; Inoue, Kazuhide
CORPORATE SOURCE: Section of Neuropharmacology, Division of Pharmacology, National Institute of Health Sciences, Tokyo, 158-8501, Japan
SOURCE: British Journal of Pharmacology (1999), 128(7), 1497-1504
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of the present study is to characterize the role of spinal

endogenous ATP and P2X receptors in the generation of neurogenic and inflammatory pain. We examined the effects of intrathecal treatment with P2X receptor antagonists on the formalin- and capsaicin-induced nociceptive behaviors in mice. Intrathecal pretreatment with the general P2 receptor antagonist, pyridoxal-phosphate-6-azophenyl-2',4'-disulfonic acid (PPADS), significantly suppressed both the first and second phases of the formalin-induced nociceptive behavior. The second phase of the nociceptive response was also suppressed by intrathecal treatment with PPADS after the first phase. Furthermore, pretreatment with the selective antagonist for the P2X1, P2X3 and P2X2+3 receptors, 2',3'-O-(2,4,6-trinitrophenyl)ATP (TNP-ATP), significantly reduced the first phase, but not the second phase. The second phase was also not suppressed by intrathecal TNP-ATP after the first phase. Capsaicin-induced nociceptive behavior that has been shown to be a model for neurogenic pain, was also significantly suppressed by intrathecal pretreatment with PPADS or TNP-ATP. Nociceptive behavior in the first phase of the formalin test and in the capsaicin test were significantly inhibited by intrathecal pretreatment with α,β-methylene ATP (α,βmeATP: 5 μg mouse-1) 15 min prior to injection of formalin or capsaicin. This treatment has been previously shown to desensitize spinal P2X3 receptor subtypes in vivo. These findings suggest that spinal endogenous ATP may play a role in (1) the formalin- and capsaicin-induced neurogenic pain via the PPADS- and TNP-ATP-sensitive P2X receptors which are also desensitized by α,βmeATP (perhaps the P2X3 receptor subtype) and (2) formalin-induced inflammatory pain via PPADS-sensitive, TNP-ATP- and α,βmeATP-insensitive P2X (and/or P2Y) receptors.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 26 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:699621 CAPLUS

DOCUMENT NUMBER: 132:91131

TITLE: Transduction and transmission properties of primary nociceptive afferents

AUTHOR(S): Treede, R.-D.

CORPORATE SOURCE: Inst. of Physiology and Pathophysiology, Johannes Gutenberg Univ., Mainz, D-55099, Germany

SOURCE: Rossiiskii Fiziologicheskii Zhurnal imeni I. M. Sechenova (1999), 85(1), 205-211
CODEN: RFZSFY; ISSN: 1029-595X

PUBLISHER: Nauka

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 45 refs. The prototypical primary nociceptive afferent is the polymodal C-fiber nociceptor, which responds to noxious thermal, mech., and chemical stimuli. C-fiber nociceptors are peripheral terminals of small neurons in the dorsal root ganglia (DRG). DRG neurons must therefore supply their peripheral terminals with the mol. machinery for the encoding of noxious stimuli into trains of action potentials. The following phenomena are known for this encoding process in vivo: (1) adaptation: for a constant stimulus intensity the action potential discharge decreases slowly within 2-3 s, (2) fatigue: recovery from adaptation may take ten minutes or more, (3) sensitization: preceding tissue damage enhances the response, particularly to heat stimuli. Recent studies in vitro have provided important clues about the mol. mechanisms underlying these phenomena. Several membrane receptors and channels are specifically expressed in small nociceptive neurons, such as vanilloid receptors (VRI), purinergic receptors (P2X3), acid sensing ion channels (ASIC), and TTX-resistant Na-channels. In the near future, we may therefore expect major advances in our understanding of the transduction of noxious stimuli into generator potentials and transformation into trains of action potentials. Along the axon that

leads from the innervated tissue to the spinal cord, primary nociceptive afferents have a limited capacity to transmit high impulse rates, suggesting a different composition of voltage-gated channels than in other primary afferents (low-threshold mechanoreceptors and thermoreceptors). Finally, the DRG neuron also supplies its central terminals with the mol. machinery for synaptic transmission and its presynaptic modulation. Progress in understanding the cellular mechanisms at both ends of the primary nociceptive neuron promises to lead to new analgesic treatment modalities for both acute and chronic pain.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 27 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:123816 CAPLUS
DOCUMENT NUMBER: 130:279598
TITLE: Cell type-specific ATP-activated responses in rat dorsal root ganglion neurons
AUTHOR(S): Ueno, Shinya; Tsuda, Makoto; Iwanaga, Toshihiko; Inoue, Kazuhide
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, Fukuoka University, Fukuoka, 814-0180, Japan
SOURCE: British Journal of Pharmacology (1999), 126(2), 429-436
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of our study is to clarify the relationship between expression pattern of P2X receptors and the cell type of male adult rat (Wistar) dorsal root ganglion (DRG) neurons. We identified the nociceptive cells of acutely dissociated DRG neurons from adult rats type using capsaicin sensitivity. Two types of ATP-activated currents, one with fast, the other with slow desensitization, were found under voltage-clamp conditions. In addition, cells with fast but not slow desensitization responded to capsaicin, indicating that there was a relationship between current kinetics and capsaicin-sensitivity. Both types of neurons were responsive to ATP and α, β methylene-ATP (α,βmeATP). The concentration of α,βmeATP producing half-maximal activation (EC50) of neurons with fast desensitization was less (11 μM) than that of neurons with slow desensitization (63 μM), while the Hill coeffs. were similar. Suramin and pyridoxal-phosphate-6-azophenyl-2',4'-disulfonic acid tetrasodium (PPADS) antagonized α,βmeATP-induced currents in both types of neurons. In situ hybridization revealed that small cells of the DRG predominantly expressed mRNAs of P2X3, and medium-sized cells expressed mRNAs of P2X2 and P2X3. In contrast, both mRNAs were not detected in large cells of the DRG. These results suggest that capsaicin-sensitive, small-sized DRG neurons expressed mainly the homomeric P2X3 subunit and that capsaicin-insensitive, medium-sized DRG neurons expressed the heteromultimeric receptor with P2X2 and P2X3.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s purinergic
L12 8266 PURINERGIC

=> s minodronic or ym 529 or ym-529 or yh 529 or yh-529 or yh529 or minodronate or minodronic acid hydrate or diphosphonate
40 MINODRONIC
2621 YM
4103 529
13 YM 529
(YM(W)529)

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          2621 YM
          4103 529
            13 YM-529
                 (YM(W)529)
          1575 YH
          4103 529
            10 YH 529
                 (YH(W)529)
          1575 YH
          4103 529
            10 YH-529
                 (YH(W)529)
            13 YH529
            31 MINODRONATE
            40 MINODRONIC
       4410376 ACID
         86859 HYDRATE
             2 MINODRONIC ACID HYDRATE
                 (MINODRONIC(W)ACID(W)HYDRATE)
          2479 DIPHOSPHONATE
L13       2574 MINODRONIC OR YM 529 OR YM-529 OR YH 529 OR YH-529 OR YH529 OR
               MINODRONATE OR MINODRONIC ACID HYDRATE OR DIPHOSPHONATE

=> s minodronic or ym 529 or ym-529 or yh 529 or yh-529 or yh529 or minodronate or
minodronic acid hydrate
            40 MINODRONIC
          2621 YM
          4103 529
            13 YM 529
                 (YM(W)529)
          2621 YM
          4103 529
            13 YM-529
                 (YM(W)529)
          1575 YH
          4103 529
            10 YH 529
                 (YH(W)529)
          1575 YH
          4103 529
            10 YH-529
                 (YH(W)529)
            13 YH529
            31 MINODRONATE
            40 MINODRONIC
       4410376 ACID
         86859 HYDRATE
             2 MINODRONIC ACID HYDRATE
                 (MINODRONIC(W)ACID(W)HYDRATE)
L14         97 MINODRONIC OR YM 529 OR YM-529 OR YH 529 OR YH-529 OR YH529 OR
               MINODRONATE OR MINODRONIC ACID HYDRATE

=> s l14 and l12
L15          0 L14 AND L12

=> s l13 and l12
L16         16 L13 AND L12

=> d ibib hitstr abs l16 1-16

L16  ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         1997:61437  CAPLUS
DOCUMENT NUMBER:          126:127245
TITLE:                    Study of nonspecific cation channel coupled to P2z
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purinergic receptors using an acid load technique

AUTHOR(S): Lachish, M.; Alzola, E.; Chaib, N.; Metioui, M.; Grosfils, K.; Kabre, E.; Moran, A.; Marino, A.; Dehaye, J.P.

CORPORATE SOURCE: Fac. Health Sci., Ben-Gurion Univ., Beer Sheva, 84105, Israel

SOURCE: American Journal of Physiology (1996), 271(6, Pt. 1), C1920-C1926
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The intracellular pH (pHi) of rat submandibular cells was measured by 2',7'-bis(carboxyethyl)-5(6)-carboxyfluorescein (BCECF). The cells recovered from ammonium (30 mM) prepulse to their resting pHi within 10 min. Ethylisopropylamiloride (EIPA), an inhibitor of the Na+/H+ exchanger, slows the rate of pHi recovery. ATP (1 mM), in the presence of EIPA, increases the rate of recovery 3.7-fold in the absence or presence of ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid. The recovery was blocked by the addition of 5 mM Mg2+ or 10 μM Coomassie blue. The response was elicited by 2'- and 3'-O-(4-benzoylbenzoyl)-ATP but not by ADP, UTP, adenyl (β-γ-methylene)-diphosphonate, 2-methylthioadenosine 5'-triphosphate, or muscarinic or β-adrenergic agonists. The purinergic response was also observed when the cells were acidified by sodium propionate and could not be mimicked by the depolarization of the plasma membrane. Aluminum fluoride did not reproduce the response to ATP, suggesting that the observed response does not involve a high-mol.-weight GTP-binding protein. It is concluded that the activation of P2z receptors, probably by the opening of nonspecific cation channels, increases the permeability to protons in rat submandibular glands.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:300566 CAPLUS

DOCUMENT NUMBER: 124:336420

TITLE: Hydrolysis of P2-purinoceptor agonists by a purified ectonucleotidase from the bovine aorta, the ATP-diphosphohydrolase

AUTHOR(S): Picher, Maryse; Sevigny, Jean; D'Orleans-Juste, Pedro; Beaudoin, Adrien R.

CORPORATE SOURCE: Fac. Sci., Univ. Sherbrooke, Sherbrooke, QC, Can.

SOURCE: Biochemical Pharmacology (1996), 51(11), 1453-1460
CODEN: BCPCA6; ISSN: 0006-2952

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Pharmacologists are becoming more and more aware of the possibility that certain ATP analogs currently used to classify the P2-purinoceptors are dephosphorylated by ectonucleotidases. In this study, the authors provide evidence that in the vascular system, these purine analogs are hydrolyzed by an ATP-diphosphohydrolase (ATPDase). This enzyme is known as the major plasma membrane nucleotidase of endothelial and smooth muscle cells, and it believed to dephosphorylate extracellular triphospho- and diphosphonucleosides. Assays were conducted with a purified ATPDase from smooth muscle cells of bovine aorta. At a concentration of 250 μM, adenosine 5'-(α,β-methylene) triphosphonate (α,β-metATP), adenosine 5'-(β,γ-methylene) triphosphonate (β,γ-metATP), adenosine 5'-(α,β-methylene) diphosphonate (α,β-metADP), adenylyl 5'-(β,γ-imido) diphosphonate (β,γ-metATP), adenosine 5'-O-(2-thiodiphosphate) (ADPβS) all resisted

dephosphorylation, whereas 2-chloroadenosine triphosphate (2-chloroATP), 2-methylthioadenosine triphosphate (2-MeSATP) and 8-bromoadenosine triphosphate (8-bromoATP) were hydrolyzed at 99, 63, and 20% of the rate of ATP hydrolysis, resp. All the non-hydrolyzable analogs tested, except α,β-metADP, competed with ATP and ADP for the ATPDase catalytic site, reducing their hydrolysis by 35-50%. Apparent Km values for ATP and ADP were estimated at 14.1 and 12.0 μM, resp., whereas apparent Km and Ki values for the purine analogs ranged from 12 to 28 μM. These results strongly support the view that (1) the ATPDase is expected to reduce substantially the P2-response induced by ATP, ADP, and some hydrolyzable agonists; and (2) by competing with the hydrolysis of endogenously released ATP and ADP, non-hydrolyzable analogs could alter the amplitude or direction of the cellular response induced by these natural substrates.

L16 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1995:723951 CAPLUS
DOCUMENT NUMBER: 123:194630
TITLE: Does interstitial adenosine mediate acute hibernation of guinea pig myocardium?
AUTHOR(S): Gao, Zhi-Ping; Downey, H Fred; Fan, Wen-Lin; Mallet, Robert T.
CORPORATE SOURCE: Health Science Center, University of North Texas, Fort Worth, TX, 76107-2699, USA
SOURCE: Cardiovascular Research (1995), 29(6), 796-804
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: The aim was to test the role of interstitial adenosine in protective downregulation of myocardial energy demand during myocardial hibernation. Methods: Isolated working guinea pig hearts, perfused with glucose fortified Krebs-Henseleit, were subjected to 60 min global low flow ischemia followed by 30 min reperfusion. Left ventricular performance was assessed from heart rate-developed pressure product and pressure-volume work. Cytosolic energy level was indexed by creatine phosphate and ATP phosphorylation potentials measured in snap frozen myocardium. Lactate and purine nucleosides (adenosine, inosine) were measured in venous effluent. Results: When coronary flow was lowered by 80% for 60 min, heart rate-pressure product and pressure-volume work fell 87% and 75%, resp., and stabilized at these low levels, but fully recovered when flow was restored. Myocardial ATP phosphorylation potential fell by 67% during the first 10 min of ischemia, but subsequently recovered to pre-ischemic levels despite continuing ischemia, indicating down-regulation of myocardial energy demand. Lactate release increased about 10-fold during ischemia and remained increased until reperfusion. Purine nucleoside release varied reciprocally with phosphorylation potential, peaking at 10 min of ischemia, then gradually returning to the pre-ischemic level during the subsequent 50 min of ischemia. The ecto 5'-nucleotidase inhibitor α,β-methylene adenosine 5'-diphosphonate (50 μM) decreased ischemic purine nucleoside release by 41%, but did not attenuate post-ischemic contractile recovery. The unspecific adenosine receptor antagonist 8-p-sulfophenyl theophylline (8-SPT, 20 μM) doubled ischemic lactate release and lowered coronary venous purine nucleoside release by 21%. 8-SPT increased phosphorylation potential at 10 min ischemia relative to untreated hearts, but blunted the subsequent rebound of phosphorylation potential. 8-SPT treatment during ischemia resulted in a significantly higher cytosolic phosphorylation potential at 30 min of reperfusion, but did not affect postischemic contractile function. Conclusions: the authors conclude that activation of adenosine receptors results in recovery of cytosolic energy level of moderately ischemic working myocardium, but this energetic recovery is not solely responsible for postischemic contractile recovery.

L16 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1995:458049 CAPLUS
DOCUMENT NUMBER: 122:205856
TITLE: Effects of suramin on contractions of the guinea pig vas deferens induced by analogs of adenosine 5'-triphosphate
AUTHOR(S): Bailey, S. J.; Hourani, S. M. O.
CORPORATE SOURCE: School Biological Sciences, University Surrey, Guildford, Surrey, GU2 5XH, UK
SOURCE: British Journal of Pharmacology (1995), 114(6), 1125-32
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English

AB ATP and some of its analogs contract the guinea pig vas deferens, acting via receptors which have been classified as P2x-purinoceptors. The authors have recently shown, however, that the effects of ATP are enhanced, rather than inhibited, by the nonselective P2 antagonist, suramin, and that this enhancement could not easily be explained in terms of inhibition by suramin of the breakdown of ATP. The authors therefore investigated the effects of suramin on contractions induced by ATP analogs, to define the structure-activity relationships of the suramin-resistant response. In the absence of suramin, the order of potency for ATP analogs was adenosine 5'-(α,β-methylene)triphosphonate (AMPCPP) = P1,P5-diadenosine pentaphosphate (Ap5A) = adenosine 5'-tetraphosphate (Ap4) > adenosine 5'-O-(3-thiotriphosphate) (ATPγS) = adenylyl 5'-(β,γ-methylene) diphosphonate (AMPPCP) > P1,P4-diadenosine tetraphosphate (Ap4A) > adenosine 5'-O-(2-thiodiphosphate) (ADPβS) > 2-methylthioadenosine 5'-triphosphate (MeSATP) ≥ ATP > ADP. This is generally in agreement with previously reported structure-activity relationships in this tissue. In the presence of suramin (1 mM), responses to Ap5A, Ap4A, AMPPCP, ADPβS and ADP were abolished or greatly reduced, and contractions induced by AMPCPP, Ap4 and ATPγS were inhibited. Contractions induced by MeSATP however, like those induced by ATP itself, were not reduced, but at concns. >100 μM were enhanced. In the presence of suramin (1 mM) the order of potency of analogs was therefore AMPCPP = Ap4 > ATP = MeSATP > ATPγS, with all other analogs tested being essentially inactive at concns. up to 500 μM. Contractile responses of the vas deferens to transmural nerve stimulation (1-50 Hz) in the presence of the α-adrenoceptor antagonist, phentolamine (10 μM), were abolished by suramin (1 mM). This is in agreement with previous reports that suramin inhibits the excitatory junction potential, a response thought to be mediated by P2 purinoceptors. It is however hard to reconcile the evidence implicating ATP as the nonadrenergic transmitter responsible for this response with the failure of suramin to inhibit the contractions induced by ATP itself while abolishing nerve-mediated contractions. In conclusion, these results confirm the previous findings of a suramin-resistant component to the ATP-induced contraction in the guinea pig vas deferens, and show that the structure-activity relationships of this response are not identical to those of any known P2-purinoceptor subclass. Although the inhibition by suramin of the breakdown of ATP may contribute to the suramin-resistance of some of the ATP analogs, it does not appear to provide the full explanation.

L16 ANSWER 5 OF 16 CAPLUS 
ACCESSION NUMBER: 1993:205421 CAPLUS
DOCUMENT NUMBER: 118:205421
TITLE: Effects of analogs of adenine nucleotides on increases in intracellular calcium mediated by P2T-purinoceptors on human blood platelets
AUTHOR(S): Hall, D. A.; Hourani, S. M. O.
CORPORATE SOURCE: Sch. Biol. Sci., Univ. Surrey, Guildford/Surrey, GU2

relatively high concns. of the antagonist required indicated that these receptors are of the A2 subtype. The P2-selective antagonist suramin (300 μM) inhibited responses to AMPCPP, but not to other agonists. The dephosphorylation of the nucleotides was studied by high performance liquid chromatog. following incubation with the longitudinal muscle preparation of up to 30 min. ATP was rapidly degraded, largely to adenosine, and AMPPCP and AMPCPP were also degraded, although more slowly, to adenosine and adenosine 5'-(α,β-methylene) diphosphonate (AMPCP) resp. AMPCP, like AMPCPP, caused relaxations by acting on P2-purinoceptors, as it was also inhibited by suramin (300 μM). Incubation of the tissue with adenosine deaminase abolished responses to adenosine, reduced those to ATP and AMPPCP, but had no effect on those to AMPCPP. ATP and AMPPCP therefore appear to be acting on the A2 receptors in this tissue largely via their degradation product adenosine. The longitudinal muscle of the rat colon therefore contains both P1- and P2-purinoceptors, which both mediate relaxation. The P1-purinoceptors are of the A2 subtype and the P2-purinoceptors are probably of the P2Y subtype, although the rapid degradation of the nucleotides means that it is difficult to classify them with certainty.

L16 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:188477 CAPLUS
DOCUMENT NUMBER: 116:188477
TITLE: Characterization of P1-purinoceptors on rat duodenum and urinary bladder
AUTHOR(S): Nicholls, J.; Hourani, S. M. O.; Kitchen, I.
CORPORATE SOURCE: Sch. Biol. Sci., Univ. Surrey, Guildford/Surrey, GU2 5XH, UK
SOURCE: British Journal of Pharmacology (1992), 105(3), 639-42
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The P1-purinoceptors mediating relaxation of the rat duodenum and inhibition of contraction of the rat urinary bladder were characterized by adenosine and its analogs 5'-N-ethylcarboxamidoadenosine (CGS 21680), as well as the A1-selective antagonist 1,3-dipropyl-8-cyclopentylxanthine (DPCPX). The stable analog of ATP, adenylyl 5'-(β,γ-methylene) diphosphonate (AMPPCP), was also used as previous work indicated that it has a direct action on some P1 receptors in addition to its P2-purinoceptor activity. In the rat duodenum, the order of potency of the adenosine agonists was NECA ≥ CPA > AMPPCP = adenosine > CGS 21680, and DPCPX antagonized CPA and AMPPCP at a concentration of 1 nM whereas equivalent antagonism of NECA and adenosine required a concentration of 1 μM. This suggests the presence of a mixture of A1 and A2 receptors in this tissue, with CPA and AMPPCP acting on the A1 and NECA and adenosine acting on the A2 receptors. In the rat bladder, the order of potency of the adenosine agonists for inhibition of carbachol-induced contractions was NECA » adenosine > CPA = CGS 21680, and a concentration of DPCPX of 1 μM was required to antagonize responses to NECA and adenosine. This suggests the presence of A2 receptors in this tissue. ATP and AMPPCP each caused contractions which were not enhanced by DPCPX (1 μM) which suggests that in this tissue AMPPCP was acting only via P2 receptors and had no P1 agonist activity. That AMPPCP was active on the A1 receptors in the duodenum but inactive on the A2 receptors in the bladder implies that it has selectivity for the A1 subtype. That CGS 21680, which has been reported to bind selectively to the high affinity A2a subclass of A2 receptors, had a very low potency on the A2 receptors in the duodenum and in the bladder suggests that these receptors are of the low affinity A2b subclass.

L16 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:171046 CAPLUS
DOCUMENT NUMBER: 116:171046
TITLE: Characterization of the P1-purinoceptors mediating

5XH, UK
SOURCE: British Journal of Pharmacology (1993), 108(3), 728-33
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB By use of a number of analogs of adenine nucleotides, the structure-activity relations of the human platelet receptor for ADP mediating increases in intracellular Ca were investigated, and compared with the known structure-activity relations for induction by ADP of platelet aggregation. ADP, 2-methylthioadenosine 5'-diphosphate (2-methylthio-ADP), adenosine 5'-O-(1-thiodiphosphate)(ADP-α-S), and adenosine 5'-O-(2-thiodiphosphate) (ADP-β-S) each induced increases an intracellular Ca in a manner similar to their reported ability to induce human platelet aggregation. The effects of these agonists were antagonized by ATP, with a pA2 value in each case consistent with the inhibition by ATP of ADP-induced aggregation. In the case of ADP, the inhibition by ATP of increases in intracellular Ca was shown to be competitive by Schild anal. Of the analogs tested as inhibitors of the effect of ADP on intracellular Ca, 2-chloroadenosine 5'-triphosphate (2-chloro-ATP), adenosine 5'-O-(1-thiotriphosphate) (ATP-α-S), P1,P5-diadenosine pentaphosphate (Ap5A), and adenylyl 5'-(β,γ-methylene)diphosphonate were apparently competitive antagonists, although only one concentration of each antagonist was used. There was a good correlation between the pA2 values found here for these antagonists, including ATP, and their pA2 values reported for inhibition of ADP-induced aggregation. Adenosine 5'-(α,β-methylene)triphosphonate and UTP (100 μM) were only very weak inhibitors of the effect of ADP on intracellular Ca, and this is consistent with their weak actions as inhibitors of aggregation. 2-Methylthioadenosine 5'-triphosphate (2-methylthio-ATP) (50 μM) noncompetitively inhibited the effect of ADP on intracellular Ca, in a very similar way to its inhibition of ADP-induced aggregation. The good correspondence found for these analogs between their effect on intracellular Ca and on aggregation confirms that there is a causal relation between these actions of ADP, and that they are mediated by the same receptor on platelets. These findings cast further doubt on the use of the affinity reagent 5'-fluorosulfonylbenzoyladenosine (FSBA) as an antagonist and label for the ADP receptor, as this compound has been reported to inhibit aggregation but not ADP-induced increases in intracellular Ca.

L16 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:208353 CAPLUS
DOCUMENT NUMBER: 116:208353
TITLE: Effects of purines on the longitudinal muscle of the rat colon
AUTHOR(S): Bailey, S. J.; Hourani, S. M. O.
CORPORATE SOURCE: Sch. Biol. Sci., Univ. Surrey, Guildford/Surrey, GU2 5XH, UK
SOURCE: British Journal of Pharmacology (1992), 105(4), 885-92
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Adenosine and ATP have been reported to cause relaxation of the rat colon longitudinal muscle preparation; the purinoceptors mediating this effect were investigated by use of a series of agonists and antagonists. The tissue was precontracted with carbachol (1 μM), and the purines induced reversible relaxations with a potency order of 5'-N-ethylcarboxamidoadenosine (NECA) > N6-cyclopentyladenosine (CPA) = adenosine 5'-(α,β-methylene) triphosphate (AMPCPP) > adenosine = adenylyl 5'-(β,γ-methylene) diphosphonate (AMPPCP) = ATP. The P1-selective antagonist 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) (3 μM) shifted to the right log concentration-response curves of all these agonists except for AMPCPP, indicating that they all act via P1-purinoceptors. The order of potency of the adenosine analogs and the

contraction of the rat colon muscularis mucosae
AUTHOR(S): Bailey, S. J.; Hickman, D.; Hourani, S. M. O.
CORPORATE SOURCE: Sch. Biol. Sci., Univ. Surrey, Guildford/Surrey, GU2 5XH, UK
SOURCE: British Journal of Pharmacology (1992), 105(2), 400-4
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous studies had shown that adenosine and adenine nucleotides including ATP caused contraction of the rat colon muscularis muscosae via P1 and P2Y-purinoceptors resp., and that the stable ATP analog adenylyl 5'-(β,γ-methylene) diphosphonate (AMPPCP) had an unexpected direct action on the P1-purinoceptors. Therefore, the P1-purinoceptors were further characterized by use of the adenosine analogs 5'-N-ethylcarboxamidoadenosine (NECA) and N6-cyclopropyladenosine (CPA) and the antagonist 1,3-dipropyl-8-cyclopentylxanthine (DPCPX), which is selective for the A1 subtype. The P2-purinoceptor antagonist suramin was also used, to investigate the selectivity of the P2 agonists. The order of potency of P1 agonists for contraction was CPA > NECA > AMPPCP ≥ adenosine, and DPCPX (1nM) caused >2-fold shifts to the right of the log concentration-response curves for each of these agonists, although the shifts were not always parallel and Schild anal. of the inhibition of the effect of adenosine resulted in a plot with a slope greater than unity. These results indicate the P1-purinoceptor mediating contraction of the A1 subtype, as has been found in other tissues in which adenosine causes contraction. The P2-purinoceptor antagonist suramin (300 μM) had no effect on the responses to adenosine or to AMPPCP, but abolished contractions induced by the related stable ATP analog adenosine 5'-(α,β-methylene)triphosphonate (AMPCPP). Contractions induced by ATP, which were not affected by DPCPX (10nM) alone, were only partially inhibited by suramin (300 μM), revealing an A1 component to its action which could be blocked by DPCPX (10 nM). Thus, the rat colon muscularis mucosae possesses contractile A1 receptors in addition to the previously characterized P2Y receptors, and the stable ATP analog, AMPPCP, has an unexpected direct action on these A1 receptors.

L16 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:1097 CAPLUS
DOCUMENT NUMBER: 116:1097
TITLE: Direct effects of adenylyl 5'-(β,γ-methylene)diphosphonate, a stable ATP analog, on relaxant P1-purinoceptors in smooth muscle
AUTHOR(S): Hourani, S. M. O.; Bailey, S. J.; Nicholls, J.; Kitchen, I.
CORPORATE SOURCE: Sch. Biol. Sci., Univ. Surrey, Guildford/Surrey, GU2 5XH, UK
SOURCE: British Journal of Pharmacology (1991), 104(3), 685-90
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous results obtained with the rat colon muscularis mucosae, which contracts in response to adenosine and had suggested that adenylyl 5'-(β,γ-methylene) diphosphonate (AMPPCP), a stable ATP analog, acted on P1-purinoceptors rather than, as expected, on P2-purinoceptors. This possibility has been examined in 2 tissues in which adenosine and ATP both cause relaxation, the guinea pig tenia ceci and the rat duodenum. ATP, 2-methylthio-ATP (2-MeSATP), AMPPCP, adenosine 5'-α,β-methylene)triphosphonate (AMPCPP), and adenosine each relaxed the tenia ceci and the duodenum, and the order of potency of the nucleotides in each tissue was 2-MeSATP > ATP > AMPCPP > AMPPCP, indicating that these effects were mediated by P2γ-purinoceptors. The P1 antagonist 8-(p-sulfophenyl)theophylline (8-SPT) (100 μM) did not affect the responses to ATP, 2-MeSATP, or AMPCPP in either tissue, but inhibited the responses of adenosine and of AMPPCP in both tissues. In

the duodenum a lower concentration of 8-SPT caused a parallel shift to the right of the concentration-response curve to adenosine and to AMPPCP but to different extents, with AMPPCP being inhibited more powerfully than adenosine. A dose-ratio of around 5 was observed for adenosine and AMPPCP at concns. of 8-SPT of 20 μM and 2 μM, resp., but Schild anal. resulted in plots with slopes greater than unity. In the tenia ceci, however, 8-SPT inhibited adenosine more powerfully than AMPPCP, and a range of concns. (10-20 μM) only caused a 2-fold shift in the concentration-response curve for AMPPCP, although the concentration-response curve to adenosine was shifted in a concentration-dependent manner and Schild anal. gave a pA2 value of 5.13 with a slope of 0.90. As has been shown in other tissues, including the guinea pig tenia ceci, ATP (100 μM) was rapidly dephosphorylated by enzymes present in the rat duodenum, with less than 10% remaining after 20 min incubation, whereas AMPPCP (100 μM) was resistant to degradation, with greater than 90% remaining at the same time point. AMPPCP therefore has pronounced but variable agonist actions on P1-purinoceptors, and appears to act entirely via these receptors on the rat duodenum although in the guinea pig tenia ceci this action is less important and it acts largely via P2γ-purinoceptors. These P1-purinoceptor effects of AMPPCP are direct and are not due to its degradation to adenosine.

L16 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:581321 CAPLUS
DOCUMENT NUMBER: 115:181321
TITLE: Human neutrophils have a novel purinergic P2-type receptor linked to calcium mobilization
AUTHOR(S): Merritt, Janet E.; Moores, Kitty E.
CORPORATE SOURCE: SmithKline Beecham Pharm., Welwyn/Herts., AL6 9AR, UK
SOURCE: Cellular Signalling (1991), 3(3), 243-9
CODEN: CESIEY; ISSN: 0898-6568
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Stimulation of suspensions of fura-2-loaded human neutrophils with ATP resulted in an elevation in cytosolic free calcium concentration ([Ca2+]i) from a basal value of 0.1 μM to a transient peak of 1 μM. The response is due to Ca2+ release from intracellular stores and influx of extracellular Ca2+. Release from intracellular stores is shown by the response in the absence of extracellular Ca2+. The greater and more maintained response in the presence of extracellular Ca2+ is indicative of stimulated Ca2+ entry and a stimulated influx pathway was confirmed by using Mn2+ as a surrogate for Ca2+. A variety of purinergic agonists were used to characterize the pharmacol. of this [Ca2+]i response. Their rank order of potency was ATP > adenosine 5'-O-(3-thiotriphosphate) (ATPγS) > ADP » 2-methylthioadenosine 5'-triphosphate (2MeSATP), where ATP had an EC50 value of 3 μM and 2MeSATP had an EC50 value of 1000 μM. Adenosine 5'-O-(2-thiodiphosphate) (ADPβS), adenylyl (α,β-methylene)- diphosphonate (AMPCPP) and adenosine were inactive at 1 mM. These results suggest that neutrophils have a novel type of purinergic P2 receptor that is neither P2x nor P2y.

L16 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:456437 CAPLUS
DOCUMENT NUMBER: 113:56437
TITLE: P2-, but not P1-purinoceptors mediate formation of 1,4,5-inositol trisphosphate and its metabolites via a pertussis toxin-insensitive pathway in the rat renal cortex
AUTHOR(S): Nanoff, Christian; Freissmuth, Michael; Tuisl, Elisabeth; Schuetz, Wolfgang
CORPORATE SOURCE: Inst. Pharmacol., Univ. Vienna, Vienna, A-1090, Austria

SOURCE: British Journal of Pharmacology (1990), 100(1), 63-8
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The adenosine receptor (P1-purinoceptor) agonists N6-cyclopentyladenosine and N-5'-ethylcarboxamidoadenosine at concns. <10 μM affected neither basal, nor noradrenaline- and angiotensin II-stimulated formation of inositol 1-phosphate, inositol 1,4-bisphosphate, and inositol 1,4,5-trisphosphate in slices of rat renal cortex. In contrast, adenine nucleotides (P2-purinoceptor agonists) markedly stimulated inositol phosphate formation. The observed rank order of potency adenosine-5'-O-(2-thiodiphosphate) (EC50 39 μM) > adenosine-5'-O-(3-thiotriphosphate) (587) ≥5'-adenylylimidodiphosphate (App(NH)p, 899) > adenylyl-(β,γ-methylene)- diphosphonate (4181) was consistent with the interaction of the compds. with the P2y-subtype of P2-purinoceptors. AMP and the ADP analog (α,β-methylene)-ADP were ineffective. ATP and ADP (≤10 mM) did not produce a consistent increase, due to their hydrolytic degradation in the incubation medium. Whereas the inositol phosphate response to APP(NH)p was linear only ≤5 min incubation, the time-dependent stimulation of noradrenaline declined at a slower rate. Following pre-exposure of the renal cortical slices to App(NH)p, renewed addition of App(NH)p caused no further enhancement in the accumulation of inositol phosphates, whereas noradrenaline was still capable of eliciting a response. Evidently apparent loss of responsiveness to app(NH)p is not due to substrate depletion or enzymic inactivation, but is most likely attributable to homologous desensitization of the purinoceptor. Pretreatment of the animals with pertussis toxin caused a substantial reduction of functional G1-protein, as indicated by the lack of [32P]NAD incorporation in a membrane preparation of the renal cortex. Nevertheless, the increase in inositol phosphate formation induced by noradrenaline, angiotensin II, and App(NH)p was not impaired. Thus, P2y-purinoceptors are present in the renal cortex; these receptors stimulate formation of inositol phosphates via a pertussis toxin-insensitive pathway and undergo homologous densensitization. On the other hand, these results suggest that renal A1-adenosine receptors do not use stimulation of phosphoinositide breakdown as a transmembrane signaling system.

L16 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:108334 CAPLUS
DOCUMENT NUMBER: 110:108334
TITLE: Receptors for ATP in rat sensory neurons: the structure-function relationship for ligands
AUTHOR(S): Krishtal, O. A.; Marchenko, S. M.; Obukhov, A. G.; Volkova, T. M.
CORPORATE SOURCE: A. A. Bogomolets Inst. Physiol., Kiev, 252024, USSR
SOURCE: British Journal of Pharmacology (1988), 95(4), 1057-62
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pharmacol. properties of the ATP-activated conductance in isolated sensory neurons of the rat were investigated by voltage clamp and concentration clamp techniques. ATP, ADP, CTP, CDP and some derivs. activate these receptors, whereas AMP, CMP, and other naturally-occurring nucleotides are competitive blockers. In the sequence of substances, adenosine 5'-(β,γ-methylene)triphosphonate (APPCP), adenosine 5'-(β,γ-difluoromethylene)triphosphonate (APPCF2P), adenosine 5'-(β,γ-dichloromethylene)triphosphonate (APPCC12P), and adenosine 5'-(β,γ-dibromomethylene)triphosphonate, the properties. of ligands depend on the radius of the atom linked to the C of the diphosphonate group. Thus, APPCP is an agonist, APPCF2P is a partial agonist, while dichloromethylene and dibromomethylene analogs of adenosine 5'-(β,γ-methylene)triphosphonate demonstrate features of competitive blockers. APPCC12P is the most effective blocker of

ATP-receptors (inhibition constant Ki = 21 μM). An adenosyl or adenylyl radical, when connected to the terminal phosphate of ATP, converts the agonist into a partial agonist. Two important parts of the ATP mol. are crucial for the interactions with receptors. They are: (1) the vicinity of C6 of the purine ring and (2) the polyphosphate chain. Some modifications in these regions of the mol. result in the transformation of an agonist into an antagonist.

L16 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1985:197812 CAPLUS
DOCUMENT NUMBER: 102:197812
TITLE: L-AMP-PCP, an ATP receptor agonist in guinea pig bladder, is inactive on taenia coli
AUTHOR(S): Hourani, Susanna M. O.; Welford, Laurence A.; Cusack, Noel J.
CORPORATE SOURCE: King's Coll., Univ. London, London, WC2R 2LS, UK
SOURCE: European Journal of Pharmacology (1985), 108(2), 197-200
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB L-Adenyl 5'-(β,γ-methylene) diphosphonate (L-AMP-PCP) [3469-78-1], a potent ATP [56-65-5] receptor agonist in the guinea pig bladder, was tested on the guinea pig taenia coli. L-AMP-PCP, unlike ATP, did not relax the taenia coli, and it neither enhanced nor inhibited the action of ATP. Unlike ATP, L-AMP-PCP was not degraded by ectonucleotidases on the taenia coli. The lack of pharmacol. effect of L-AMP-PCP on the taenia coli supports the suggestion that the ATP receptors here differ from those in the guinea pig bladder.

L16 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1983:69404 CAPLUS
DOCUMENT NUMBER: 98:69404
TITLE: Stimulation of renal gluconeogenesis by exogenous adenine nucleotides
AUTHOR(S): Saggerson, E. David; Carpenter, Carol A.; Veiga, Jose A. S.
CORPORATE SOURCE: Dep. Biochem., Univ. College London, London, WC1E 6BT, UK
SOURCE: Biochimica et Biophysica Acta, General Subjects (1983), 755(1), 119-26
CODEN: BBGSB3; ISSN: 0304-4165
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tubule fragments were isolated from renal cortex of fed rats. Gluconeogenesis from lactate was significantly increased by low concns. of exogenous ATP, ADP, AMP, adenylyl (β,γ-methylene) diphosphonate, and, to a lesser extent, by ITP and inosine. GTP was slightly inhibitory. Exogenous adenosine deaminase slightly decreased gluconeogenesis, and its effect was additive to that of GTP. Adenosine deaminase did not abolish the stimulatory effects of ATP or cAMP. ATP (40 μM) also stimulated gluconeogenesis from pyruvate, malate, succinate, 2-oxoglutarate, and glutamine, but had no effect when glycerol or fructose were used as substrates. With lactate as substrate, the effect of 40 μM ATP was additive to the maximal stimulations of gluconeogenesis seen with 1 μM noradrenaline or 0.1 μM angiotensin II, but was not additive to the stimulatory effect of 0.1 mM cAMP. ATP (40 μM) had no effect upon either the tubule content of cAMP or upon 45Ca efflux from prelabeled tubules. Addition of ouabain or removal of extracellular K+ diminished the stimulatory effects of ATP and cAMP. Extracellular ATP was rapidly metabolized by tubule fragments, with resulting accumulation of adenosine. Further metabolism resulting in formation of inosine, hypoxanthine, xanthine, and uric acid was also observed CAMP was metabolized less rapidly, with no accumulation of adenosine. The effects of

purinergic agents on gluconeogenesis are discussed.

L16 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1983:65990 CAPLUS
DOCUMENT NUMBER: 98:65990
TITLE: Modulation of the release of acetylcholine from ileal synaptosomes by adenosine and adenosine 5'-triphosphate
AUTHOR(S): Reese, James H.; Cooper, Jack R.
CORPORATE SOURCE: Dep. Pharmacol., Yale Univ., New Haven, CT, 06510, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1982), 223(3), 612-16
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Low concns. of either adenosine (I) [58-61-7] or ATP [56-65-5] inhibited the nicotine-induced release of 3H-labeled acetylcholine [51-84-3] from synaptosomes derived from the guinea pig ileum myenteric plexus. I and ATP were equipotent in their ability to inhibit the release, and the inhibition was reversible by theophylline in both cases. ATP may have acted after initial hydrolysis to I and the receptor involved may be the P1 or similar R site receptor. High concns. of ATP caused marked increases in the release of [3H]acetylcholine. This release was neither temperature- nor Ca-dependent. Because the concns. required were similar, however, to those which have been reported to cause ATP-induced contractions in intact prepns., further studies of the phenomenon were carried out. Lactate dehydrogenase was not released with the [3H]acetylcholine, suggesting that indiscriminate lysis of the membranes had not occurred. The release was not affected by theophylline, indomethacin, tetrodotoxin, or I. The ATP analog adenylyl (β,γ-methylene)- diphosphonate did not cause the increase in release, therefore phosphorylation may be required for the effect. The mechanism of increased release remains to be defined, but the data suggest that it is unlikely that a P2 receptor is involved.

L16 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1982:98343 CAPLUS
DOCUMENT NUMBER: 96:98343
TITLE: Evidence for the presence of P1-purinoceptors on cholinergic nerve terminals in the guinea pig ileum
AUTHOR(S): Moody, Catherine J.; Burnstock, Geoffrey
CORPORATE SOURCE: Dep. Anat. Embryol., Univ. Coll. London, London, WC1E 6BT, UK
SOURCE: European Journal of Pharmacology (1982), 77(1), 1-9
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The inhibitory effects of adenosine [58-61-7], ATP [56-65-5], 5'-adenylyl methylene diphosphonate (β,γ-meATP) [3469-78-1], and adenosine 5'-α,β-methylene triphosphonate (α,β-meATP) [7292-42-4] were compared on the cholinergic twitch responses to transmural stimulation of the guinea pig ileum. Adenosine, ATP, and β,γ-meATP reduced the twitch responses in a concentration-dependent manner. Theophylline antagonized and dipyridamole potentiated the inhibitory responses to adenosine, ATP, and β,γ-meATP. Inhibitory responses to α,β-meATP were usually preceded by an enhancement in twitch height. Contractions of the unstimulated ileum to α,β-meATP were blocked by atropine and tetrodotoxin, whereas those elicited by ATP were unaffected; this suggested that the initial excitatory effects of α,β-meATP may be due to its ability to release acetylcholine from cholinergic nerve terminals. Use of high pressure liquid chromatog. and bioluminescence assay techniques demonstrated the ability of the tissue to degrade ATP, β,γ-meATP, and, at a much slower rate, α,β-meATP.

Inhibitory responses to ATP, AMP [61-19-8], and β,γ-meATP were reduced by adenosine deaminase, which also abolished responses to adenosine. 5'-AMP deaminase abolished responses to AMP and adenosine and reduced those to ATP and β,γ-meATP. Apparently, the inhibitory effect of ATP on cholinergic neurotransmission is due to its rapid breakdown to AMP or adenosine, which act on prejunctional P1-purinoceptors.